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BIODESIGN

EXOGENOUS SIALIDASE-INDUCED DESIALYLATION OF BLOOD PLASMA LOW-DENSITY LIPOPROTEINS IN MICE

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Objective: Sialidases can contribute significantly to atherosclerosis development due to their ability to modify low-density lipoproteins (LDL). An association of desialylated LDL with atherosclerosis progression was found several decades ago. Nevertheless, the detailed information about all factors causing LDL desialylation is still to be clarified. A proper model can help with the understanding of the factors causing LDL desialylation. The task of the study was to create a model of desialylation of LDL in mice upon an injection of immobilized sialidase.

Methods: The experimental group of wild type C57BL6 mice (n=48) received bacterial (*Vibrio cholerae)* sialidase conjugated with mouse IgG (the control group of C57BL6 mice was subjected to a single injection of saline). Termination of mice was carried out at fixed periods of time before and after single injection (1-7 days). Ultracentrifugation was applied for LDL isolation from serum, and then the content of sialic acid was detected using Warren's method as well as lipids of serum were identified using commercially available kits.

Results: Up to 30%-decrease of LDL sialylation was found up to 5 days after sialidase injection with no change of serum levels of triglycerides, total cholesterol and HDL-cholesterol.

Conclusions: A new model of LDL desialylation *in vivo* was established using mice and exogenous sialidase. This model can help with research of factors affecting sialylation of lipoproteins in blood. Research was supported by the Russian Science Foundation (grant#20-15-00264).

GINGIVA- AND ADIPOSE-DERIVED MSC SPHEROIDS SURVIVABILITY AND FUNCTIONALITY AFTER 3D BIOPRINTING

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Mesenchymal stromal cells (MSCs) are the most commonly used cell type for 3D bioprinting, including those based on spheroids. MSCs have a wide range of biological properties that differ depending on the cell source. The aim of the current work is to compare important parameters of bioprinted MSC spheroids, such as survivability, metabolic activity, proliferation rates, migration and differentiation, depending on the cell source.

Bioink for 3D extrusion bioprinting consisted of hydrogel and spheroids. The the hydrogel included gelatin, fibrin modified with acrylated polyethylene glycol (PEG), and riboflavin. Spheroids were formed from MSCs isolated either from the subcutaneous adipose tissue or alveolar mucosa of gingiva. Bioprinting was performed with BioX CellInk 3D extrusion bioprinter, and obtained constructs were cultured up to 21 days.

The printed constructs were viable and metabolically active, but the rates of cell proliferation differed depending on cell source. Adipose tissue MSCs migrated faster in the hydrogel, forming extensive cell clusters. Gingival MSCs developed longer, thinner, and more branched sprouts.

Thus, constructs based on adipose tissue/gingival MSC spheroids obtained by 3D bioprinting differ by a number of functional and morphological properties. Understanding of each specific population features would allow to optimize biofabrication strategies, providing high cell density and survivability of 3D bioprinted constructs.

The study was supported by the Russian Foundation for Basic Research (№ 22-75-10120, 3D bioprinting, hydrogels).

CHANGES IN THE BRONCHOPULMONARY SYSTEM OF RATS WITH EXPERIMENTAL METABOLIC SYNDROME

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Metabolic syndrome (MetS) is a factor promoting the development of bronchopulmonary pathology. Progressive increase in the prevalence of MetS in the population necessitates the study of its role during the development of bronchopulmonary dysfunction. It is known that visceral obesity, hyperinsulinemia, hyperglycemia, and dyslipidemia contribute to the development of bronchial hyperreactivity.

The MetS model was performed on male Wistar rats (n=33). Rats were separated into control and experimental groups. The rats from the control group were fed standard rat chow. The rats of the experimental group had a high-fat, high-carbohydrate diet for 12 weeks. The biochemical parameters of the blood, the concentration of cytokines IL-6, IL-10, TNF-α in the blood and lavage fluid, and the contractile activity of the bronchi were evaluated. A histological examination of the bronchi of rats was performed.

In rats of the experimental group classical signs of the MetS were found, as well as an increase in the concentration of TNF-α, IL-10 in the serum, and IL-6 in the lavage fluid. It was shown that MetS was associated with an increase of bronchoconstrictor action of carbacholine (0.1-100 μM) and a decrease of the dilatory effect of salbutamol (0.1-100 μM). Histological examination revealed destruction of the bronchial epithelium, signs of immune inflammation in the bronchial wall. The study was funded by the Council for Grants of the President of the Russian Federation (CS-3302.2022.1.4).

CONCENTRATION OF MAGNETIC NANOPARTICLES IN POLYELECTROLYTE SHELLS AS KEY TO CONTROL THE RESONANT FREQUENCY OF THE RELEASE UNDER LOW FREQUENCY MAGNETIC FIELD IRRADIATION

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The use of a low-frequency magnetic field (LFMF) is a promising method for controlling the permeability of magnetically sensitive polyelectrolyte microcapsules. With such an impact, heating does not occur, and the energy of the magnetic field is converted into rotational motion of the magnetic nanoparticle inside the shell. Such movement can cause deformation of the shell, thereby increasing its permeability.

Polyelectrolyte magnetically sensitive microcapsules were prepared by the layer-by-layer method. The shell of microcapsules includes 6 layers of oppositely charged polymers (poly (allylamine hydrochloride) and poly (styrene sulfonate)) and 1 layer of magnetic nanoparticles (MNP), which was in the middle between them. In experimental part of work, we showed that the maximum release of the encapsulated model substance occurs at different frequencies (50 and 77 Hz) for different batches of capsules. In computer modeling we demonstrated that under the influence of the LFMF rotation of MNP have a resonant character. Additionally, we showed that increase in the force acting from the side of the microcapsules shell on MNP leads to an increase in the frequency of the magnetic field, at which the rotation amplitude of the MNP reaches a maximum. We assume that changing of concentration of magnetic nanoparticles in the microcapsules shell, allows to control the value of the resonant frequency.

This work was supported by the grant of the President of the Russian Federation (MK-1109.2021.1.3).

HYPOCHLOROUS ACID IS THE MAJOR OXIDANT CAPABLE OF DEGRADING PERICARDIUM SCAFFOLDS IN SUSPENSION OF ACTIVATED NEUTROPHILS

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In tissue engineering, scaffolds provide mechanical support and biochemical signals to ensure cell survival and differentiation. The synergy of the immune response and scaffold degradation processes largely determines the efficiency of tissue regeneration. We demonstrated previously the degradation of decellularized bovine pericardium (DBP) in suspension of activated neutrophils. Activated neutrophils produced high redox reactive oxygen species which are capable to oxidize biomaterials such as pericardium scaffolds: superoxide anion, hydroxyl and hydroperoxyl radicals, and hypochlorous acid (HOCl) — the major product of myeloperoxidase. Here, we studied the effectiveness of oxidizing agents in modification of DBP crosslinked with genipin (DBPG). In model system, superoxide radicals formed in xanthine oxidase catalyzed reaction did not oxidize DBPG. As shown by atomic force microscopy, hydroxyl and hydroperoxyl radicals formed in the Fenton reaction were 7-8 times less effective in modification of DBPG surface than hypohlorite (NaOCl). We employed multiphoton tomography combined with fluorescence lifetime imaging (FLIM) to study scaffold modification in a suspension of neutrophil activated by phorbol myristate acetate. The DBPG degradation was completely blocked in the presence of methionine which is a scavenger of HOCl with the formation of a stable end product of methionine sulfoxide. Our results show that hypochlorous acid is a main oxidizing agent that can modify and degrade pericardium scaffolds at the sites of inflammation.

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PHAGOCYTE ACTIVATION BY 3D POLYLACTIDE-BASED SCAFFOLD

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The implantation of materials initiates the development of local inflammation, in which the coordinated action of the cells of immune system ensures effective tissue regeneration. The physicochemical properties of scaffolds are known to influence the functional response of immune cells. Here, we studied the phagocyte activation by synthetic material, the 3D polylactide-based structure fabricated using two-photon polymerization (PLA-2Ph), and compared the results with those previously obtained for the natural material, decellularized bovine pericardium crosslinked with genipin (DBPG). Both materials activated neutrophils in whole blood to produce reactive oxygen species as revealed by luminol-dependent chemiluminescence and flow cytometry and induced myeloperoxidase secretion. Formation of neutrophil extracellular traps-like structures on the surface of both scaffolds and in blood was demonstrated. In contrast to DBPG, PLA-2Ph did not promote the polarization of THP-1 macrophages into the classically activated M1 state as shown by measuring the concentration of pro-inflammatory cytokines in cell culture media. We compared the ability of the studied materials to be oxidized by hypochlorite, the main oxidant produced by activated neutrophils. While atomic force microscopy demonstrated oxidation of DBPG surface at physiologically relevant concentrations of NaOCl, modification of PLA-2Ph by oxidant was not revealed. We used scanning electron microscopy to detect PLA-2Ph surface modification at high concentrations of NaOCl. Our study demonstrates different effects on macrophages, but similar level of neutrophil activation by synthetic and natural materials and their different ability to be modified by phagocyte-derived oxidants.

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THE CONTENT OF MCP-1 IN THE BLOOD SERUM OF PATIENTS WITH EARLY STAGES OF PRIMARY OSTEOARTHRITIS OF THE KNEE JOINT

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Objective. To study the serum level of MCP-1 in patients at the onset of primary osteoarthritis of the knee joint.

Material and methods. Main group — 20 patients with early primary gonarthrosis stages (10 men and 10 women); the controls were 20 apparently healthy individuals without diseases of musculoskeletal system (13 men and 7 women). Determination of content studied indicator was carried out by the method of enzyme-linked immunosorbent assay on automatic multifunctional photometer EpochTM (Biotek, USA). For statistical processing of variational series, the method of non-parametric statistics was used with the calculation of the Mann-Whitney test, the level of statistical significance was accepted as $p<0.05$.

Results. In patients of the main group (0-I stages of gonarthrosis), the content of MCP-1 increased 2.72-fold in the blood serum ($p<0.05$) as compared to the control group. This fact, according to F. Ni et al. associated with its ability to produce a large number of pro-inflammatory cytokines, performing an osteoresorptive function.

Conclusion. Changes in blood serum of MCP-1 content in patients at onset of primary osteoarthritis of the knee joint may reflect pathogenetic mechanisms of this pathological process formation.

APPLICATION OF OPTICAL SPECTROSCOPY METHODS FOR DIAGNOSTICS OF EARLY OSTEOARTHRITIS

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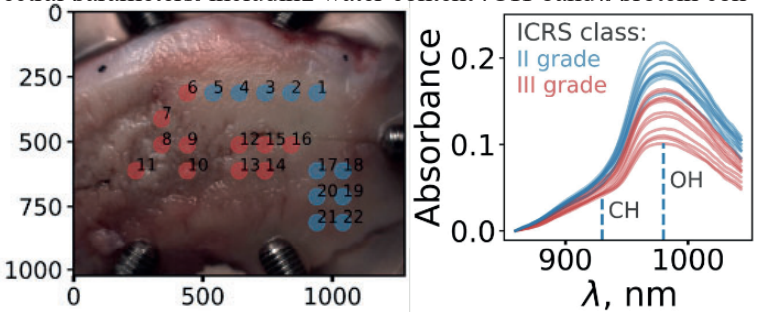
Osteoarthritis (OA) is one of the most common joint diseases worldwide. Unfortunately, clinical methods lack the ability to detect OA in the early stages. Timely detection of the knee joint degradation at the level of tissue changes can prevent its progressive damage.

The explants of 11 patients with OA were studied. Diffuse reflectance spectroscopy (DRS) in the NIR range was used to obtain optical markers of the cartilage damage grades and to assess its mechanical properties. The degree of damage was analyzed at the mapping points, the obtained optical and mechanical data were divided into four groups according to the degree of cartilage degradation.

It was observed that the water content obtained by DRS strongly correlates with the cartilage thickness (R = .82) and viscoelastic relaxation time (R = .7). Moreover, the spectral parameters, including water content (OH-band), protein content (CH-band), and scattering parameters allowed for discrimination between the cartilage damage grades ($10^{-4} < P \leq 10^{-3}$).



The developed approach may become a valuable addition to arthroscopy, helping to identify lesions at the microscopic level in the early stages of OA and complement the surgical analysis.

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IONIC-ELECTROACTIVE POLYMERS IN BIOMEDICAL APPLICATIONS

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Ionic polymer-metal composites (IPMC) possess a number of useful properties such as flexibility, light weight, high degree of biocompatibility, low energy consumption [1,2]. IPMC has the ability to act as both a strain gauge and an actuator. At the same time, as a sensor of an IPMC product, it does not require a power source. Biomedical applications of IPMC include: ptosis treatment implant, artificial ventricle, sphincters and eye muscles, artificial smooth muscle drives, correction of the refractive index of the human eye, peristaltic pumps, active catheters, assistive devices for urinary incontinence and various surgical instruments.

Commonly, IPMC presents in a “sandwich” form, where the layers alternate: metal, polymer, electrolyte, polymer, metal. All components (materials, frames) are required to correspond a high degree of biocompatibility for its invasive use. For this purpose, noble metal films (platinum, gold) are used because of low-toxic effect for living cells, that is why, they serve as electrodes, but the flexibility decreases.

We analyzed the literature materials regarding such electrodes using in medical devices. It was found that the most suitable films are based on biocompatible composite nanomaterials containing bovine serum albumin (BSA — matrix) and multi-walled carbon nanotubes (MWCNT — filler), carboxylmethylcellulose (CMC — matrix) and (MWCNT — filler) [3].

Литература

1. Indeed, the films of discussed composite nanomaterials have a high degree of biocompatibility, as their matrices consist of biological materials and fillers of carbon nanotubes (<10 wt.%) are functionalized by biological BSA or CMC molecules, and they practically do not leave the matrix. In BSA/CNT and CMC/CNT films the surface resistance is ≤ 0.04 μBauer S. Proc. SPIE 10163, Electroactive Polymer Actuators and Devices (EAPAD) 2017, 1016303 (1 May 2017).
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THERMAL METHODS OF THERAPY IN ORTHOPEDICS AND ONCOLOGY

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Thermal therapy has been widely developed in oncology and orthopedics [1,2]. There is an increasing trend towards the combined use of the following therapies: photothermal (PTT), photodynamic (PDT), and hyperthermic (HTT) with the use of magnetic nanoparticles (MNPs).

We have carried out a comparative analysis of these methods.

1. Laser PTT is limited by low spatial selectivity, which is partially solved by using various photosensitizers (PS), namely, gold nanoparticles. The latter are characterized by ease of preparation, low local toxicity, and approximation of tumor heating kinetics calculations relative to other antitumor agents, for example, quantum dots.
2. Photothermal agents should have several basic properties, such as: strong absorption of light in the near infrared range (extinction coefficient value $>10^5$ M^{-1}. The PDT method makes it possible to use various drugs as PS, the molecules of which are susceptible to light and are destroyed when exposed to laser radiation. With the optimal selection of the type of PS, wavelength and intensity of laser radiation, it is possible to achieve a therapeutic effect — the death of cancer cells. Under certain conditions, the process of PDT therapy can be carried out in an outpatient clinic and in daylight [4].

PDT is characterized by some side effects on the skin: swelling in or near the treated area, discoloration, itching, tingling or burning, skin infections.

PTT and PDT can be used in combination with other methods introduced into practical medicine, however, there are a number of contraindications to radical and palliative treatment, for example, allergic reactions to PS.

3. HTT is based on overheating of the target tissue area due to magnetization reversal of superparamagnetic NPs in an external alternating magnetic field. Multifunctional MNPs serve as agents for: vector drug delivery, diagnostics, and therapy. MNPs in vivo can effectively inhibit and kill cancer cells, including metastasized ones, if the parameters of the GTT mode are correctly selected [5].

The HTT efficiency depends on many parameters of MNPs, including sizes (5–1000 nm), shape (spherical, rod, disk), thickness, type of coating material, and magnetization values. Preclinical and clinical studies are underway to explore the use of various thermometric methods in temperature monitoring of bone cancer HTT. This is particularly relevant because of the vulnerable structures adjacent to bone tissue (e.g., spinal cord and nerve roots) [6].

HTT is not yet sufficiently optimized, but is being actively investigated and is already gradually moving into the phase of clinical trials.

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EXTRACELLULAR VESICLES REDUCE M1 MACROPHAGE POLARIZATION

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The control of inflammatory process during wound healing is an important challenge of regenerative medicine. At the initial stage of inflammation, neutrophils and M1 macrophages produce reactive oxygen species (ROS) and pro-inflammatory cytokines. Changing phenotype of macrophages from M1-proinflammatory to M2-anti-inflammatory is a key step determining the wound healing, since M2-macrophages contribute to the resolution of inflammation. Several studies have shown that extracellular vesicles (EV), such as matrix-bound nanovesicles (MBV) and exosomes, are able to modulate the inflammation by influencing the polarization of macrophages. The aim of this study was to evaluate immunomodulatory effect of EV on the polarization of human M1 macrophages. EV obtained from 3T3 fibroblasts were added to macrophages together with polarization inducers into M1 phenotype — IFN-γ+LPS. ELISA revealed that MBV and exosomes reduced production of proinflammatory marker TNF-α in the M1-macrophages compared to control cells receiving only IFN-γ+LPS. Enzymes (collagenases) used for isolation of MBV did not affect the production of TNF-α by macrophages. Therefore, the registered effect is determined only by EV. Additionally, incubation of macrophages with exosomes caused the decrease in ROS production by M1 macrophages compared with control cells as assayed by chemiluminescence. Our study showed that EV obtained from 3T3 fibroblasts are able to polarize M1 macrophages towards the macrophage phenotype, which has reduced pro-inflammatory activity, accompanied by a decrease in the formation of ROS and proinflammatory cytokines.

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FABRICATION OF SCAFFOLDS FOR BIOACTIVE MOLECULES IN ANTISOLVENT DEPOSITION OF POLYLACTOGLYCOLIDE SOLUTIONS BY 3D-PRINTING

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Introduction. The production of bioactive materials to fill extended bone defects requires an integrated approach. One is associated with the acquisition of biocompatible and resorbable porous scaffolds of a defined shape with an internal structure that ensures cell adhesion, proliferation, and differentiation in the presence of a bioactive components. We have developed a

method for antisolvent 3D printing of matrix structures from a solution of aliphatic copolyesters in a non-toxic tetraethylene glycol solvent as a new approach to solving this problem. The architectonics of the produced porous structure depends on the phase decomposition conditions of homogeneous poly (lactic-co-glycolic acid) polymer in tetraethylene glycol mixtures.

Materials and methods. The macrostructure and shape of the polymer samples were set by a digital three-dimensional printing. The nature of the microporous structure formed during the phase decomposition of polymer mixtures was established by changing the temperature setting of the phase separation process.

Results. It was shown that depending on the temperature in a constant ratio of components in the initial mixture, the architectonics of the sample can vary from a homogeneous monolith to systems with interpenetrating pores with 90% free volume. In most cases, the microstructure of the sample had a significant anisotropy. Depending on the fabrication conditions, the shapes of the pores changed from symmetric to finger-shaped and their combinations. It was possible to form both submicron pores and reaching sizes of several hundred micrometers. Thus, the use of the thermally induced phase separation is an effective way to control the microstructure of polymer matrices.

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CHONDROGENIC DIFFERENTIATION OF WHARTON'S JELLY-DERIVED MESENCHYMAL STEM CELLS FOR CELL SHEET PRODUCTION

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Cell sheet engineering has been used for regeneration of different tissues including hyaline cartilage. Our study aimed to adjust the existing mesenchymal stem cells (MSCs) chondrogenic differentiation protocols for obtaining the scaffold-free cartilage-like tissue-engineered constructs.

Wharton's jelly-derived MSCs were isolated from tissues of four different patients and subsequently used as a mix after performing the flow cytometry and trilinear differentiation test. The cells were expanded until passage 5 and seeded on fibrous matrices electrospun from thermoresponsive polymer pNIPAM-NtBa. After cultivation in chondrogenic differentiation medium for 3 weeks, the cell sheets were collected via dissolvement of matrices. Resveratrol and either LiCl or Y27632 were used as additional components for expansion and differentiation culture medium correspondingly.

Resveratrol was shown to enhance cell expansion with no influence on cell differentiation. The obtained cell sheets were 50-100 μm-thick and 5-7 mm in diameter. Toluidine blue and safranin O histological staining was slightly positive and comparable in all the samples. According to immunohistochemical analysis, transcription factor SOX9 was almost equally expressed in investigated samples. LiCl ones were superior to others in collagens type I and type II accumulation, while Y27632 ones contained less collagen type II, but were almost free of collagen type I. Chondrocyte hypertrophy marker MEF2C was predominantly found in LiCl samples.

The analysis showed that the combination of expansion medium with resveratrol and differentiation medium with Y27632 allows for obtaining cell sheets with positive chondrogenic markers with no signs of hypertrophy.

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LASER CELL TRANSFECTION USING GOLD NANOPARTICLE LAYERS FOR CONTROLLED GENE DELIVERY

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The development of reliable technologies for introducing external nucleic acids to the cells of interest is one of the priority tasks of modern bioengineering. A broad list of research studies are devoted to the development of novel delivery systems or investigation of the present technologies [1] based on various carriers and/or with the use of physical forces [2]. However, there is still no universal technology that should be at once safe, compatible with different cell types and delivered agents, scalable and cost-effective.

Recently we proposed a new gene delivery system called plasmonic-induced cell optoporation [3]. The basic principle relies on a short-term increase in the permeability of cell membranes adhered on Au nanoparticles layers (AuNPl) due to the short-term local heating of particles induced by a NIR laser irradiation in a resonant mode. AuNPl were obtained directly on cultural plastic, which is an excellent cell-friendly substrate [4]. The main advantage of the system is the ability to precise adjustment of the individual characteristics of cells and delivered agents by tuning both the irradiation regimes and parameters of AuNPl. We defined the excellent capabilities of our system for a number of mammalian cells contrasting in transfection properties (HeLa, A431, CHO, RAW 264.7) and delivered agents of a wide size range, such as molecular dyes and control plasmids.

Thus, we believe that the developed system is an extremely promising tool for *in vitro* cells transfection, ready-to be adapted for complexed objects, such as primary and stem cells. In addition, the scale-up ability opens prospects for practical transfer for tasks of gene therapy and cellular bioengineering.

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MSCS' CONDITIONED MEDIA NAVIGATES HUMAN MACROPHAGES TOWARDS ANTI-INFLAMMATORY PHENOTYPE

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There is a growing body of evidence that secretome of multipotent mesenchymal stromal cells (MSCs) possesses a high potential to modulate inflammatory processes and regeneration via complex crosstalk with immune cells, including macrophages. This research was aimed to study the effects of MSCs' secretome on polarization of human macrophages, since switching the balance between pro- and anti-inflammatory macrophages phenotypes is one of the key stages of tissue repair. The composition of conditioned media obtained after cultivation of different types of MSCs were analyzed by multiplex immunoassay. Umbilical cord-MSCs' conditioned media (UMSCs-CM) were used because of a high concentration of some cytokines, which are predominantly pro-inflammatory molecules, including IL-6 and IL-8. Macrophages were obtained by differentiation of monocytes isolated from the blood of healthy volunteers. ELISA revealed a significant decrease in a concentration of the standard pro-inflammatory macrophage marker TNF-α in supernatants of M1 macrophages after their treatment by UMSCs-CM comparing to control. Moreover, according to the flow cytometry data, incubation of M2 macrophages with UMSCs-CM led to a significant increase of surface expression of the major anti-inflammatory macrophage marker CD206 (mannose receptor). Strong correlations were observed between concentration of cytokines in UMSCs-CM and macrophage polarization. Taken together, these results suggest that despite their mostly pro-inflammatory cytokine profile UMSCs-CM are able to promote macrophages' polarization to anti-inflammatory M2 state.

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ANALYSIS OF GWAS FOR ABDOMINAL WALL HERNIAS

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Currently, only 2 GWAS with anterior abdominal wall hernias have been performed in the world so far (Jorgenson E. et al. 2015, Wei J. et al. 2022). The first study was performed in USA, where 4 maximally associated polymorphisms *EFEMP1, WT1, EBF2* and *ADAMTS6* were found. The second study was conducted in the UK, 57 maximally associated polymorphisms with hernias of the anterior abdominal wall were identified. As in the first study , the second study revealed the same 4 polymorphisms that were maximally associated.

Purpose. To analyze polymorphisms of genes maximally associated with hernias of the anterior abdominal wall.

Materials and methods. Gene analysis was performed using an internet resource ww.genecards.org

Results. Polymorphisms *EFEMP1, WT1, EBF2* and *Adamts6* in both studies were genes maximally associated with hernias of the anterior abdominal wall. These genes perform the function of supporting connective tissue homeostasis. When analyzing 57 genes of candidates that were found in the second study, the function of 16 genes is not yet known. Collagen's genes were not found among genes.

Conclusion. It is necessary to conduct GWAS in other populations to more accurately determine the maximum associated genes with hernias of the anterior abdominal wall.

COVALENT PLGA MODIFICATION FOR FLUORESCENT IMAGING AND TARGETED DELIVERY OF NANOSYSTEMS

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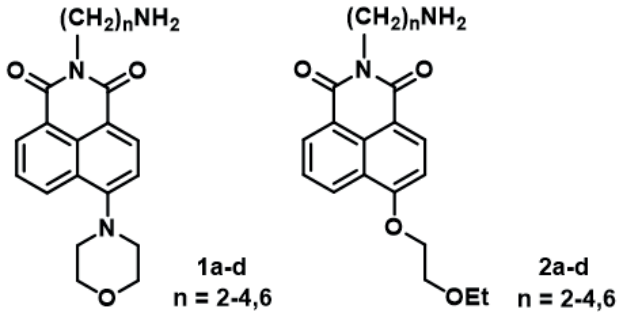
The covalent introduction of fluorescent dyes into PLGA opens up new possibilities for bioimaging, because such systems can be useful for studying the biodistribution in the body, the features of pharmacokinetics and pharmacodynamics during *in vivo* experiments. In the present work, covalent modification of PLGA with fluorescent derivatives of 1,8-naphthalimide with varying spacer lengths between the naphthalimide core and the terminal amino group was carried out. The resulting polymers were subsequently used to prepare fluorescent nanoparticles.



In this work the spectral and luminescent properties of markers based on 1,8-naphthalimide derivatives emitting fluoresce in the blue and green regions of the spectrum and featuring different length spacer between the terminal amino group and the naphthalimide moiety were investigated. Application of fluorophores exhibiting maximum absorption in the 375–405 nm region provides an opportunity to use super resolution techniques with the highest excitation efficiency, which makes it possible to achieve a resolution equal to half the wavelength of the excitation light.

The particles obtained using PLGA-**1d**, PLGA-**2a**, and PLGA-**2d** conjugates displayed the finest spectral properties with the highest brightness. The stability of the obtained particles was studied in PBS, RPMI-1640, and DMEM media. It was demonstrated that the particles are stable in these media.

In summary, the covalently modified 1,8-naphthalimide derivatives obtained in this work are considered very promising for a wide range of challenges in fluorescent imaging and targeted drug delivery.

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ВОЗМОЖНОСТИ КЛЕТОЧНОЙ ТЕРАПИИ В РЕКОНСТРУКЦИИ РУБЦОВЫХ ПОРАЖЕНИЙ ГОЛОСОВЫХ СКЛАДОК

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Одной из частых причин нарушения голосовой функции является рубцевание голосовых складок (ГС). В настоящее время не существует метода для восстановления морфофункциональных свойств поврежденной ткани. Клеточная терапия открывает новые перспективы в этом направлении.

Целью исследования являлось изучение потенциала мезенхимных стромальных клеток (МСК), полученных из костного мозга человека, в восстановлении морфологических и механических характеристик ГС при рубцевании in vivo.

Экспериментальная модель включала формирование дефекта ГС и имплантацию клеточного продукта через 3 месяца путём инъекции во вторичную рану после иссечения рубца. В эксперименте было задействовано 30 кроликов. На основании вида имплантируемого материала были сформированы 4 группы по 6 животных: 1 группа — физиологический раствор, 2 группа — полиэтиленгликоль(ПЭГ)-фибриновый гель, 3 группа — суспензия МСК, 4 группа — комплекс МСК с ПЭГ-фибриновым гелем, в качестве группы чистого контроля были взяты 6 интактных голосовых складок из биобанка. Кролики с имплантированными МСК-GFP в суспензии и геле выводились через 3 дня после имплантации, 24 кролика из экспериментальных групп 1-4 выводились через 3 месяца.

По результатам морфологических и вибрационных исследований было выявлено, что МСК человека способствовали регенерации ГС, приближая морфологические и механические свойства к нативным, не было выявлено статистически значимых отличий от интактных голосовых складок ($p=0,898$ — МСК в комплексе с ПЭГ-фибриновым гелем). Рубцы после клеточной терапии отличались меньшей толщиной собственной пластинки ГС ($p<0,05$) и восстановлением архитектоники коллагеновых структур ($p<0,05$ — МСК с ПЭГ-фибриновым гелем).

Развитие клеточной терапии открывает новые возможности в лечении пациентов с рубцовым поражением, Полученные результаты демонстрируют регенераторный потенциал МСК при введении их во вторичную рану голосовой складки.

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ДОКЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ IN VITRO И IN VIVO БИОМЕДИЦИНСКОГО КЛЕТОЧНОГО ПРОДУКТА ДЛЯ ЗАМЕЩЕНИЯ ДЕФЕКТОВ КОЖИ

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Кожа является самым большим органом человека и животных и служит защитным барьером между организмом и окружающей средой. При обширных нарушениях целостности кожных покровов, таких как ожоги большой площади, раневые дефекты, области хирургического вмешательства, ресурсов организма не достаточно для полноценного восстановления кожного покрова. Следует отметить, что традиционные методы лечения таких повреждений часто оказываются малоэффективны и сопровождаются формированием хронических ран, гипертрофических рубцов и контрактур. Последнее диктует необходимость разработки новых способов лечения. Одним из наиболее динамично развивающихся направлений в этой области является тканевая инженерия. Разработка кожных эквивалентов ведется во всем мире. Ключевой концепцией при создании таких продуктов является использование скаффолд-технологий. Нами разработан биомедицинский клеточный продукт на основе гидрогелевого скаффолда-носителя из биополимеров с инкапсулированными стволовыми клетками.

В исследованиях in vitro показано, что скаффолд-носитель обеспечивает функцию искусственной клеточной ниши, а процессы, наблюдаемые при культивировании БМКП, сходны с естественными процессами «динами-

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ческой взаимности». Так в процессе культивирования в структуре скаффолда клетки проявляли матрикс-клеточную адгезию, трехмерный рост с образованием клеточной сети, имели развитый цитоскелет. Можно предполагать, что успешные клеточные события обеспечиваются биологически активным составом скаффолда и его структурными характеристиками. Показано, что клетки активно пролиферировали, динамично секретировали VEGF-A и изменяли структурные характеристики скаффолда. Длительное культивирование скаффолдов с инкапсулированными клетками приводило к изменению свойств биодеградации скаффолдов.

В доклинических исследованиях in vivo на модели полнослойной скальпированной кожной раны крыс показано, что БМКП, способствовал раннему формированию грануляционной ткани, ускорению процессов ангиогенеза, образованию и организации правильно упорядоченных коллагеновых волокон в подлежащей ткани, ускорению эпителизации. Полученные данные подтвердили, что эффективность применения представленного БМКП опосредована не только активностью клеток, но и биологической активностью скаффолда-носителя.

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ВЛИЯНИЕ КИСЛОТ НА МИКРОПРОВОДЫ С ЦЕЛЬЮ ИХ ЗАОСТРЕНИЯ

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Предметом исследования данной работы было селективное травление микропроводов с составом α-Fe/DyPrFeCoB кислотами и смесям кислот. Целью данной работы было создание микропроводов с вытянутой иглообразной или параболической геометрией конца для создания достаточной концентрации магнитного потока и последующим управлением магнитомечеными клетками и микроскопическими биологическими объектами без нарушения их целостности и деградации. В ходе работы микропроводы, полученные путём экстракции висящей капли расплава α-Fe/DyPrFeCoB, подвергались селективному травлению кислотами HNO_3, HCl, H_2SO_4, H_3PO_4, а также смесями кислот HNO_3 + $HClO_4$, HNO_3 + HCl (1:3), H_2SO_4 + HNO_3 (1:1). Микропроводы помещались в кислоты по 10–15 раз на 1–2 секунды с последующим промыванием дистиллированной водой и высушиванием на воздухе. Обработка результатов проводилась с использованием оптического микроскопа. В результате травления радиусы микропроводов варьировались от 1,5 мкм до 20 мкм, градиент магнитного потока находился в диапазоне 0,1874–0,6463 · 10^5 Т/м. Далее проходило исследование воздействия намагниченных микропроводов на возможность захвата и управления клетками HELA. В ходе исследования наблюдалось, что микропроводы способны захватывать и передвигать живые клетки без повреждения их целостности и нарушения мембранных структур. Это позволяет сделать вывод, что полученные в результате травления радиусы микропроводов и создаваемые им градиенты магнитного потока имеют достаточные значения для манипуляции биологическими объектами. Данные микропроводы могут служить основой для микропинцетов, которые, в свою очередь, используются в механобиологии: микрореологии, механосенсеринге, а также обеспечивают сцепление клетка-матрица и клетка-клетка. Механобиология, в свою очередь, имеет широкий спектр возможностей применения в микроскопии, медицине, исследовании и управлении микроскопическими объектами. Микропроводы, полученные с помощью селективного травления, имеют большие перспективы эксплуатации в научной деятельности различных направлений.

МЕДИЦИНСКИЕ ГАЗЫ КАК ОСНОВА ДЛЯ ИННОВАЦИОННЫХ БИОМЕДИЦИНСКИХ И ВЕТЕРИНАРНЫХ ТЕХНОЛОГИЙ

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В настоящее время большое внимание исследователей и практикующих врачей уделяется саногенетическим эффектам и возможностям применения технологий, основанных на использовании различных медицинских газов. Помимо широко применяемой в последние годы (в особенности — в период распространения новой коронавирусной инфекции) кислородной поддержки, проводимой как помощи баллонного кислорода, так и концентраторов, на протяжении нескольких десятилетий активно внедряются методы озонотерапии и гипербарическая оксигенация. Созданы предпосылки для расширения перечня потенциально полезных медицинских газов (в частности, за счет ксенона, синглетного кислорода и др.), однако для их полноценного включения в схемы лечения различной патологии требуются детальная расшифровка их биологических эффектов и патогенетическое обоснование эффективности. Кроме того, возникает вопрос о возможности и целесообразности сочетанного применения мето-

дов газ-индуцированной терапии для взаимодополнения и/или достижения синергетического эффекта. На этом основании целью работы служила систематизация фундаментальных представлений и клинико-экспериментальных данных о влиянии медицинских газов на биосистемы различного уровня организации. Критический анализ данных литературы и результаты собственных многолетних исследований авторов позволил выделить основные направления развития газ-индуцированной терапии, исходно включающие изолированное применение отдельных медицинских газов (озон, синглетный кислород, монооксид азота, инертные газы, моно- и поликомпонентная холодная плазма и др.). Сформированы принципиальные универсальные пути и механизмы их действия на биологические системы, а также специфические особенности, характерные для отдельных вариантов газ-индуцированной терапии. Высказана гипотеза, что единым механизмом восприятия различных физических воздействий, в том числе медицинских газов, является особый молекулярный сенсор, образуемый активными формами кислорода и азота и встроенный в свободнорадикальные процессы клеток. Дальнейшая расшифровка молекулярных механизмов управления окислительным метаболизмов и коррекции биорадикального стресса способна создать предпосылки для появления и развития инновационных биомедицинских и ветеринарных технологий.

БЛИЖНЕПОЛЬНОЕ СВЧ-ЗОНДИРОВАНИЕ: ПРОШЛОЕ, НАСТОЯЩЕЕ, БУДУЩЕЕ

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Медицинская визуализация в настоящее время является одним из наиболее динамично развивающихся направлений медицинской науки. Основной целью обзора является систематизация информации о текущем состоянии микроволновой визуализации биологических объектов, в первую очередь тканей организма. Проанализированы основные варианты микроволнового зондирования биологических объектов. Охарактеризованы два основных метода определения различных параметров оценки. Это микроволновая термометрия (пассивная) и резонансная томография ближнего поля. В основе обсуждения лежат физические принципы применения микроволнового зондирования. Показано, что резонансная микроволновая томография ближнего поля позволяет визуализировать структуру биологических тканей на основе пространственного распределения их электродинамических характеристик — диэлектрической проницаемости и проводимости. Показаны потенциальные области применения этого метода в дерматологии, включая дерматоонкологию. Приведены известные результаты применения метода у пациентов с дерматозами. Показана информативность технологии в ранней диагностике меланомы. Продемонстрированы перспективы микроволновой диагностики в комбустиологии, реконструктивной и пластической хирургии. Таким образом, микроволновое зондирование — это современный, динамично развивающийся метод биофизической оценки тканей организма.

Имеются убедительные доказательства целесообразности применения микроволнового зондирования в комбустиологии (в различные периоды ожоговой болезни), а также в реконструктивной хирургии, что подтверждено многолетними исследованиями нашего коллектива, выполненными на экспериментальных моделях и в клинических условиях. Также проведена серия работ, направленных на верификацию диагностической информативности ближнепольного резонансного СВЧ-зондирования в дерматологии, в том числе дерматоонкологии (меланома кожи). Начаты исследования по раскрытию возможностей данного метода в косметологии. Дальнейшие исследования в этой и других областях биомедицины значительно расширят спектр возможностей современных технологий визуализации.

СРАВНИТЕЛЬНАЯ ОЦЕНКА НЕКОТОРЫХ БИОЛОГИЧЕСКИХ ЭФФЕКТОВ ГЕЛИЕВОЙ И АРГОНОВОЙ ХОЛОДНОЙ ПЛАЗМЫ

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Одним из наиболее активно изучаемых эффектов в последние годы является холодная плазма — четвертое состояние вещества, представляющее собой ионизированный газ. Благодаря ионизации плазма приобретает особые свойства и характеристики, позволяющие реализовать ее биологическую активность. В настоящее время определены многочисленные области медицинского применения холодной плазмы, включая хирургию, дерматологию и косметологию, онкологию и др. В то же время для каждой из этих областей медицины значимы различные механизмы и эффекты фактора: антибактериальная активность, влияние на апоптоз, прорегенеративные свойства и т.д.

Целью исследования было изучение реакции свободнорадикальных процессов и антиоксидантной системы в эритроцитах крыс на курсовое применение гелиевой и аргоновой холодной плазмы. Первая группа крыс (n=10) была интактной, с ней не проводили никаких манипуляций. Крысы второй и третьей групп (n=10 в каждой) получали ежедневную обработку предварительно эпилированной задней поверхности (площадь — 4 $см^2$) потоком гелиевой и аргоновой холодной плазмы соответственно. Продолжительность каждой лечебной процедуры составляла 1 минуту, курс включал 10 процедур. В эритроцитах животных изучали перекисную резистентность, концентрацию малонового диальдегида и активность ряда ферментов (альдегиддегидрогеназы, супероксиддисмутазы и каталазы). Было обнаружено, что наружное применение холодной плазмы значительно трансформирует окислительные процессы и антиоксидантные ферменты эритроцитов, и этот эффект специфичен относительно используемого газа-носителя. Выявлено, что курс обработки поверхности кожи спины крыс гелиевой холодной плазмой способствует ограничению интенсивности свободнорадикальных процессов в мембранах эритроцитов, происходящих на фоне умеренной (физиологической) стимуляции активности антиоксидантных ферментов (супероксиддисмутазы и каталазы).. Напротив, аргоновая холодная плазма, используемая в аналогичном режиме, действует как активатор перекисного окисления липидов в клетках крови, что сопровождается выраженной дезадаптивной интенсификацией каталитических свойств антиоксидантных ферментов эритроцитов.

ФОРМИРОВАНИЕ НОВОЙ ОСИ ХИРАЛЬНОСТИ ПРИ ХЕЛАТИРОВАНИИ АМИНОКИСЛОТ ЦИНКОМ

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При исследовании оптической активности хелатов цинка с L-метионином была выявлена зависимость роста угла вращения от увеличения концентрации комплексообразователя . Были приготовлены растворы содержащие равные количества аминокислоты, и различные добавки цинка сульфата в соотношениях: 20:1, 10:1, 5:1, 2:1, 1:1, 1:2 (АМК:Zn) в изоэлектрической точке аминокислоты. Угол вращения менялся от $-0{,}15^0$ (L-метионин) до $-0{,}66^0$ (1:2). Далее данный эксперимент проводился на аминокислотах: L-валин, D-валин, DL-валин, L-изолейцин, DL-изолейцин, L-глутаминовая кислота, L-гистидин, L-аспарагиновая кислота, D-аспарагиновая кислота, DL-аспарагиновая кислота.

Результаты измерений разделились на две группы: бидентатные аминокислоты повторяли тенденцию метионина, при этом для L-валина изменялся знак угла вращения (+) на (-), и также численно увеличивалось значение угла вращения, для тридентатных аминокислот отсутствовали значимые изменения угла вращения от концентрации цинка. Также была обнаружена обратная зависимость между парами энантиомеров аминокислот: для бидентатных аминокислот D ряда при увеличении концентрации иона цинка угол вращения увеличивался в положительном значении, а L ряда в отрицательном. Для визуализации образующихся структур были использованы онлайн программы структурного моделирования молекул в 3D. Интерпретировав их, мы пришли к выводу, о том, что для хелатов содержащих бидентатные лиганды формируется новая ось хиральности, и образуются две формы комплексов: цис- и транс- изомеры, между собой являющиеся диастреомерами. На основании полученных результатов можно сделать вывод, о том, что конфигурация комплексов цинка с бидентатными аминокислотами зависит от конфигурации аминокислоты. Отсутствие значимых изменений оптической активности тридентатных аминокислот, при добавлении комплексообразователя, остается предметом последующих исследований.

IT TECHNOLOGIES IN MEDICINE

ANTIMICROBIAL PROPERTIES OF THE NANOCOATED SURGICAL SUTURES BASED ON THE ATOMIC LAYER DEPOSITION TO DECREASE SURGICAL SITE INFECTIONS

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Sutures are biomaterials that are considered a major cause of surgical site infections. Sutures account for 57% of the global surgical equipment market as the most widely used surgical implants. Surgical sutures play an important role during the wound healing of the surgical sites which are known to be sensitive to microbial infections. It has been estimated that 25 000 of Europeans die every year from bacterial infections caused by multiple drug resistance microbes [1]. Outbreaks of surgical infections and bacterial resistance against antibiotics has prompted research towards development of antibacterial biomedical materials for medical applications. For that purpose, in the present work polypropylene (PP) surgical sutures (VP-945) were coated with vanadium doped TiO_2 (Al_2O_3/$TiVO_x$) using thermal atomic layer deposition (ALD) technology to decrease surgical site infection. Sutures with antibacterial activity have been developed in the present work to prevent microbial colonization of the suture material in operative incisions. Multiple layers of (Al_2O_3/$TiVO_x$) nano-films were coated on the PP surgical sutures to improve its antibacterial properties, thereby, prevent suture-related post-surgery complications. In our previous publication [2], this material (Al_2O_3/$TiVO_x$), has been successfully used as an antibacterial nano-coating to prevent post-surgical complications of implanted PP hernia mesh. The present study indicates that ALD coating improves antibacterial properties of polypropylene (PP) surgical suture, *i.e.*, (Al_2O_3/$TiVO_x$) coated surgical suture exhibited enhanced antibacterial activity compared to uncoated one. We found that V-doping of TiO_2, unlike bare TiO_2, allows generated and further procured strong redox reactions which effectively kills bacteria under visible light. We have reported comparative analysis of the use of uncoated and coated PP surgical suture for preventing biofilms formation compared. It is shown that all tested surgical suture samples expressed antibacterial activity against *E. coli* and *S. aureus*.

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APPLICATION OF TRANSFORMERS NEURAL NETWORKS TO THE CLASSIFICATION PROBLEM OF CHRONIC VENOUS DISEASE

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Chronic venous disease (CVD) is not taken seriously by ordinary people as much as it should be. This is due to the fact that CVD does not greatly affect the human body in the early stages. That's why many people do not even realize that they have an early stage of this disease. At the same time, CVD will progress, especially

if the patient is overweight or has to sit or stand for a long time during the day. The last stage of CVD is an ulcer, which requires a long and expensive therapy. Therefore, the best way to prevent the development of CVD is to consult a certified phlebologist at an early stage of CVD. However, as mentioned above, it is practically impossible for ordinary persons to understand that they have this disease. For this reason, the proposed study devoted to the classification problem of CVD and primarily aimed at ordinary people is actual. The problem is to classify according CEAP non-professional photos taken by patients themselves on a smartphone camera. Widely used convolutional networks have not performed well enough to solve this problem. That's why visual transformers were used for solving this problem, as the most perspective and contemporary neural nets for image classification.

The dataset contained 11 118 photos of legs with different CVD stages. These photos were classified by a certified phlebologist for seven CEAP classes. Class C0 contained 7.84% of the photo; C1 -25.27%; C2 — 13.43%; C3 — 33.67%; C4 — 13.76%; C5 — 3.62%; C6 — 2.40%. Thus, the dataset was unbalanced, thereby many widely used neural networks like ResNet50 couldn't cope well with the classification of such dataset. But neural networks for image classification from the transformer's library like ViT (Visual Transformers) and DeIT (data-efficient image transformers) are good enough for imbalanced datasets. The main difference between DeIT and VIT is that DeIT is an improved version of VIT through the use of a knowledge distillation procedure.

In the proposed work, three neural networks were used — one DeIT(deit-base-distilled-patch16-224) and two VITs (vit-base-patch16-224 and vit-base-patch16-384) nets.

Vit-base-patch16-384 had the best metrics for classification of the most CEAP classes but was computationally intensive. The Vit-base-patch16-384 model shows the best results in classification for classes C5 and C6. But DeiT worked better for classification of C0 and C1 classes. The worst results were shown by vit-base-patch16-224. So, using vit-base-patch16-384 seems to be preferable if there are no limits on computing resources. Deit-base-distilled-patch16-224 can be used if computing resources are limited.

POSSIBILITY OF DIAGNOSING BREAST CANCER BASED ON CYTOKINE PROFILE USING MACHINE LEARNING METHODS

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Breast cancer is one of the most common types of cancer. More than 2 million cases of breast cancer (BC) are diagnosed every year in the world. The early diagnosis of BC is the only way to significantly increase chances of cure and survival for patients with BC. Methods for early BC diagnosis are existed, for example, mammograms, clinical breast exam and breast self-exam. But the result of such diagnosis is highly dependent on the competence of the person who conducts it. That's why the problem of developing methods for early BC diagnosis is still relevant. One of the ways to do that is using methods and algorithms of machine learning.

Possibility of diagnosing breast cancer based on cytokine profile using machine learning methods is studied in the proposed work.

As previously shown by the authors, the combination of certain cytokines in blood serum can be considered as a marker of the presence of breast cancer and even its stage (local or spread). Since the dataset was rather limited, the task of binary classification was investigated in the work — whether there is breast cancer or not. To solve this problem, the Gradient Boosting algorithm was used. The model was trained on constructed features, which are combinations of cytokines.

As a result, the classification accuracy was equal to 1. This means that the concentration of certain cytokines and their combinations can be used for diagnosis and prognosis.

The high accuracy value can be explained by the following reasons. Firstly, the model was trained on constructed features based on combinations of cytokines. Second, the initial data set was randomly divided into training and test datasets but were not statistically distinguishable. But anyway, the predictive algorithm must be tested on more numbers of patients before it can be used in practice.

FEATURES OF THE USE OF AI TECHNOLOGIES IN MEDICINE: SMART GR-CASES

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Topic on the specifics of the use of semi-autonomous systems and existing models for the implementation of AI in medicine. Features of statistical modeling and elimination of cases of obtaining «dark data» in projects on the use of AI.

At present, the technology of statistical modeling and data analysis is becoming more and more scalable. The use of «MAGIC» type technology, which allows medical professionals to perform up to 50 functional options necessary for conventional medical interventions, also includes technology — augmented reality glasses that track tasks and provide assistance to medical professionals for the correct and effective treatment of patients.

Such technologies, formalized in projects, have their pros and cons, in particular on the issue of transferring data to AI. In this regard, the promotion of such projects has its own risk factors: technical, legal and others.

Adaptation measures are needed for AI and existing databases, possible filtering tools as an applied component of AI projects in medicine.

It is proposed to consider such projects and implement them with the necessary intersectoral assessment, using centers and innovation clusters.

SEMANTIC SEGMENTATION OF BLOOD VESSEL USING DEEP LEARNING

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Angiogenesis is the development of new blood vessels from pre-existing ones. It is a complex multifaceted process occurring in the human body, underlying various physiological and pathological conditions. It is essential for the adequate functioning of the human body. The study of angiogenesis is carried out using various methods. One of the most popular and simple of these is the method of short-term culture of endothelial cells on Matrigel. However, a significant disadvantage of this method is the manual analysis of numerous images of different stages of angiogenesis, which is quite time-consuming and requires considerable labour input. Therefore, a tool to automate the annotation of blood vessel images is needed. A neural network-based model serves as such a tool. Despite the increasing use of deep learning in biomedical image analysis, there are still no works on the application of this method to angiogenesis images. This paper presents the first tool based on a convolutional U-Net coder-decoder architecture for segmenting images from in vitro angiogenesis simulations, followed by image post-processing for data analysis by experts. AngioCells, the first annotated dataset in this field, is also available in the public domain. To create this dataset, members of the marking group were recruited, an annotation protocol was developed and a participant agreement study was conducted.

MUSE — MICROSCOPY WITH ULTRAVIOLET SURFACE EXCITATION

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Traditional histology relies on physically sectioning either frozen or formalin fixed paraffin-embedded (FFPE) tissue into slices. Due to FFPE-method is time consuming and labour-intensive, there is a need for a faster and simpler ex-vivo microscopy method. MUSE — approach, relying on the principle of excitation of the tissue surface with ultraviolet (UV). A distinctive feature of MUSE is the absence of the need for standard histological preparation. UV

penetrates a few micrometers and the excitation spectrum of the fluorescent dye lies in the visible spectrum. This approach makes it possible to obtain an image comparable in informational content to standard microscopy methods.

As a result of those efforts, a staining protocol was submitted and a set of fluorescent dyes, which, in total, allow high-quality identification of the histological structures of the tissue, do not require special equipment, fixation and take about 5 minutes.

MUSE has potential utility in dermatopathology and in intraoperative assessment of surgical margins. This method expands the possibilities of using computer vision technologies in microscopy, as it provides extensive information about the structure and autofluorescence of tissue.

VR TECHNOLOGIES IN PHARMACEUTICAL EDUCATION

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Educational programs using virtual reality technology are being implemented in russian and world practice: simulators in the oil and gas industry, medicine (human anatomy, surgeon simulator), the army and the aviation industry. However, these technologies are practically not used in the pharmaceutical industry. At the same time, to date, there are no developed methodologies for building the educational process using virtual reality technology, evaluating the effectiveness and safety for students. In this regard, the goal of our project is to develop a new educational program for pharmaceutical specialists using virtual reality.

The essence of the project is the formation of professional competencies and skills of pharmaceutical specialists using virtual reality technologies.

In the Russian Federation: more than 71,000 pharmacy organizations, more than 200 pharmacy chains, which employ more than 275,000 employees with pharmaceutical education. There are 83 large industrial enterprises producing medicines and 53 universities have pharmaceutical faculties that annually graduate more than 19,000 pharmacists and more than 40,000 annually are accredited in the specialty. In total, more than 600,000 people are involved in the pharmaceutical industry.

Thus, the formation of professional competencies of pharmaceutical specialists using virtual reality technologies will improve the quality of educational services provided and will allow for more effective training (professional retraining, advanced training) of pharmaceutical workers and students.

THE PENULTIMATE STEP TOWARDS INTEGRATING ARTIFICIAL INTELLIGENCE INTO ROUTINE MEDICINE

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Recently, there have been more and more reports about the increasing burden on the healthcare system. Artificial Intelligence (AI) is a modern tool that is being actively studied for finding a solution to this problem.

Today, the market for medical AI systems is extremely poor. To finalize the creation of full-fledged competitive clinical AI tools, it is necessary to understand their actual quality.

The most reliable method of evaluating the AI models quality is external validation. This technique involves obtaining training and test datasets from different sources. External validation excludes the influence of data source features on the model's conclusions, therefore it is the most optimal.

A systematic review of the literature describing the development and evaluation of AI models predicting diseases of the knee and hip joints was conducted. The study aims to analyze trend methods for evaluating AI models and identify the place of external validation in the structure of these approaches.

Of the relevant 56 articles, only 10 (17.9%) reported external validation. This makes it possible to judge the prevailing lack of objectivity of models validation.

The dissemination of the external validation concept among AI model developers will allow science to take the penultimate step towards the full integration of AI into medicine, completing the process of developing AI tools. The last step will be the solution of complex bioethical issues, which stimulates the uncompromising integration of AI into the physician's routine.

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APPLICATION OF ARTIFICIAL INTELLIGENCE ALGORITHMS TO DETERMINE THE BOUNDARIES OF COLORECTAL CANCER FROM HISTOLOGICAL SCANS

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Introduction: Colorectal cancer is the third most common cancer in the world and the leading cause of death among gastrointestinal tumors. At the same time, in 0.8-1.6% of cases, an erroneous pathoanatomical diagnosis is recorded even by highly qualified doctors.

Objectives: To develop own digital platform for image analysis and colorectal cancer patterning in histological scans using a neural network analysis algorithm.

Material and Methods: The training sample consisted of 359 cases of colon adenocarcinoma and 711 cases of adenomatous changes. Histological preparations were scanned, and digital copies were marked by specialist doctors in the ANTSHealth digital platform into 3 classes: benign tissue, malignant tissue, and background. For training, the neural network model "Linknet_efficientnetb0" was taken. The training units were 256x256 pixel images extracted from gigapixel images of digitized preparations. Validation was carried out by selecting image samples of a fixed diameter and class by three medical specialists independently of each other. If the prevailing interpretation of the sample by the neural network model corresponded to the visual assessment of the pathologist, the observation was marked as correct. A total of 279 samples were taken.

Results: In a comparative analysis of the interpretation of histological slides performed by a neural network and a pathologist, the sensitivity of the method was 0.9974; specificity, 0.8398; accuracy — 0.9420; F1-measure — 0.9571.

Conclusion: The elaborated digital platform has confirmed its high sensitivity and specificity for the detection of colorectal cancer in histological slide scans. This platform can be applied for clinical decision support systems, telemedicine system, for training doctors.

DATABASE AS A BASIS FOR CREATING A BIORESOURCE COLLECTION AND A PATIENT'S DIGITAL TWIN

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Introduction: Databases are widely used in modern medicine and can be applied for clinical and fundamental research, for training neural networks (artificial intelligence) to analyze scans of histological slides and create a "digital twin" to personalize prognosis and therapy.

Materials and Methods: The database "Bioresource Collection of Colorectal Cancer" was created on the basis of the spreadsheet software Microsoft Excel and contained categorized data for each of the 79 patients.

Results: The elaborated database contains the following information about a patient with colorectal cancer: personal data, macroscopic and microscopic description of the surgical material, parameters of the metastatic potential of the tumor, the results of molecular genetic and immunohistochemical studies, and scans of histological slides of tumor and colorectal cancer metastases.

Conclusion: The database "Bioresource collection of colorectal cancer" is promising for implementation in clinical practice and inclusion in teaching aids of the department. The database will serve as the basis for creating a "digital twin" of a patient with colorectal cancer in order to predict the course of colorectal cancer and response to drug therapy.

DEVELOPMENT OF A WEB APPLICATION OF FACILITATE MULTIDISCIPLINARY REHABILITATION OF CHILDREN WITH A CONGENITAL PATHOLOGY OF THE MAXILLOFACIAL REGION

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In recent months the priority area of modern medicine has become on-line informatization and computerization. The most promising development has been the use of information and computer support in an integrated diagnostic system for patients with cleft lip and palate. In our research we aim to developed an autonomous web application that allows practitioners to determine the tactics of multidisciplinary diagnosis and treatment based on data integrated into a specific web application in order to increase the efficiency of the treatment of children with cleft lip and palate of different age groups. Based on more than 45 years of clinical and scientific experience in diagnosis and treatment of patients with cleft lip and palate we developed a web application "ADI" (Application of Digital Imaging) (Fig. 1.). "ADI" web application is a system for processing, accumulating and analyzing information on the rehabilitation of patients with cleft lip and palate by type of pathology and age, allowing doctors to obtain structured information about the stages of the necessary methods of interdisciplinary cleft lip and palate diagnosis and treatment. One of the main advantages of "ADI" web application is the ability to quickly exchange information between specialists in various fields of knowledge.

a b c

Fig. 1. Image of the main page of the "ADI" web application on a smartphone (a), a tablet (b) and a desktop computer (c).

DEVELOPMENT OF A PROTOTYPE INTELLIGENT DIAGNOSTIC SYSTEM FOR EMERGENCY SURGICAL PATHOLOGY AT THE PRE-HOSPITAL STAGE

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Objective: to develop a prototype intelligent diagnostic system for emergency surgical pathology at the pre-hospital stage and the principles of differential diagnosis of this pathology.

Background. The development of medical diagnostic systems requires the formalization of diagnostic criteria, a clear understanding of the sequence of diagnostic algorithms, and the creation of a unified space of attributes that are equally understood by the physician, the intelligent system, and the patient.

Formalizing the diagnostic process is a difficult task because an experienced physician "at a glance" takes into account many attributes, including not only age, gender, the position of the patient, and constitutional features, but also manifestations of emotions and reactions to questions and the examination procedure. These are largely visual characteristics, but of great importance is the intonation of the voice and the "tactile talent" of the physician.

Results. At the first stage, we identified the most significant signs sufficient for primary diagnosis of emergency surgical pathology, often referred to as "acute abdomen". To identify these signs, we formulated patient-understandable questions. The interface of the system under development will allow the patient to fill in the data on his or her own during the initial application for medical care. Or the information will be entered into the system by medical personnel before the surgeon's examination. The intelligent system will then formulate the answers received in the form of expressions accepted for filling out medical records and recommend a surgeon's examination in an emergency or other specialized specialist according to the presumed diagnosis.

Conclusion. The intelligent system under development will be able to suspect emergency surgical pathology based on a minimum number of signs, make a differential diagnosis of diseases and make recommendations on the need for an emergency consultation with a surgeon and other specialists.

LEGAL ASPECTS OF ARTIFICIAL INTELLIGENCE ERRORS IN MEDICINE

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Artificially intelligent are used extensively in medical sciences. Common applications include diagnosing patients, transcribing medical documents, treating patients... Artificial intelligence predictions are getting more and more accurate. Therefore, AI is applied more and more often, the circle of tasks solved expands.

But the probability of an error remains. Mistakes — may entail severe consequences (including the death of the patient). Who is responsible for artificial intelligence mistakes?

There are several options:

Responsibility lies with the doctor

Responsibility lies with the developer of artificial intelligence

Artificial intelligence has a legal personality and bears responsibility independently

Responsibility lies with the head of the medical organization

By agreeing to the use of artificial intelligence in diagnosis and treatment, the patient accepts responsibility

Each option has its own strengths and weaknesses. Only the professional community of doctors, lawyers and IT specialists can find the answer.

MATHEMATICAL MODELING OF THE INTERACTION OF NEW QUINAZOLINONE DERIVATIVES WITH NICOTINAMIDE ADENINE DINUCLEOTIDE IN ORDER TO PREDICT THE POSSIBILITY OF ADDUCT FORMATION AS ONE OF THE STAGES OF INHIBITION OF FATTY ACID SYNTHASE *MYCOBACTERIUM TUBERCULOSIS*

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Introduction. The resistance of *Mycobacterium tuberculosis* to the applied antimicrobial substances, and also the ability of the pathogen to remain latent in the human body for a long time complicate the therapeutic strategy for the treatment of diseases caused by the microorganism, making the problem of finding new drugs relevant. The study of the mechanism of action of medicinal substances at the molecular level has become possible due to the successes achieved in the field of bioinformatics and mathematical modeling. In this way, the all study following the ethical restrictions in the field of clinical research on animals. The formation of an adduct of a drug substance with nicotinamide adenine dinucleotide (NAD) inhibits the intense activity of the fatty acid synthase (FAS) enzyme involved in the synthesis of mycolic acids, which is natural for the presence of the cell membrane of *Mycobacterium tuberculosis* has been proven.

Purpose. Mathematical modeling of the interaction of new derivatives of quinazoline–4(3*H*)–on with NAD in order to predict their effect on the operation of FAS.

Material and methods. The modeling of the formation of complexes between VMA-17-04 and VMA-13-05 derivatives and the oxidized form of NAD^+ was carried out using the semi-empirical quantum-chemical PM7 method in the MOPAC 2016 program [1].

Results. The energies of the boundary molecular orbitals, the value of the electrophilic index, the distances between interacting atoms, the charges on the atoms, as well as the value of the energy gap were calculated for each pair of interactions.

Conclusions. An analysis of the energy and structural characteristics indicates the complexity of the formation of an intermediate complex between VMA-17-04 and NAD+ due to steric factors.

The high values of the energy of the highest occupied molecular orbital (HOMO), as well as the values of the energy gap and the distance between the interacting atoms indicate a high probability of the formation of an adduct between VMA-13-05 and NAD, which makes it possible to predict the possibility of FAS inhibition by this derivative.

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HEALTH&SCIENCE WEB APPLICATION: OPPORTUNITIES AND PROSPECTS

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Health&Science is a digital platform (Web-application) designed to digitize and systematize data on the health status of patients, quickly and conveniently compile statistical samples for the work of medical specialists, rational visits to medical organizations, remote provision of clinical recommendations, convenience of obtaining data on the health status of patients, promotion and popularization of the medical services market, updating of data.

The platform will be useful to a wide range of consumers: patients of any gender and all ages, medical professionals, medical organizations.

The development of Health&Science is aimed at meeting the need for rational visits to medical organizations, information education about health correction, maintaining a healthy lifestyle, saving time during medical research, creating high-quality visual content for use in the professional field (systematization of health data, the ability to conduct scientific and clinical work with regular customers through the service, popularization of the personality of the expert and/or medical organization, etc.), providing digital tools for upgrading users' personal accounts.

Functional sections will be implemented on the platform that subscribers will be able to use daily: health monitoring (for medical organizations — patients), analysis of survey blocks on organ systems, clinical recommendations in a convenient format, visual representation of data on the complex of examinations performed, a clear picture of the complex of upcoming studies. In addition, information sections with useful information and recommendations on health and lifestyle correction will be presented.

Another feature is that the platform is a meeting place and remote work of a doctor with a patient / medical organization with a service user / researcher and an up-to-date updated database. Users (doctors and medical organizations) can independently use the functional tabs registered on the service.

To achieve the goals and objectives of the project, an application for grant support has been submitted to the Innovation Promotion Fund in the section "Personalized Medicine. Medical decision support systems. Devices for continuous screening of patients' health. Telemedicine".

CLASSIFICATION OF METASTASIS BONE STAGES BASED ON A LIMITED NUMBER OF SCINTIGRAPHY IMAGES

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The development of an artificial intelligence decision support system for oncologists is a topical task, the solution of which will affect many patients. There are many articles with the topic of using neural networks to solve the problem of image classification, where various MRI and X-ray images are input. However, it should be noted that some classification problems are difficult to solve due to the lack of sufficient data to correctly train even the most popular and accurate neural networks. This problem is especially relevant for specific medical data. To solve this problem, certain approaches are applied to increase the size of the dataset. The most popular of these are noise overlay, image rotation, different color palettes usage, etc. As a result, the initial dataset is expanded with images that for AI are different from the existing ones.

In the proposed work, the applicability of different kinds of neural networks for the classification of the stages of metastasis bones based on a limited number of scintigraphy images was studied. The widely used convolutional networks (ResNet50) and new networks (transformers ViT and DeIT) were used in the work. The results of training these neural networks on a small amount of data were analyzed using the following metrics: accuracy, precision, recall, f1-score, confusion matrix and learning curve.

The study included 65 patients with a different stage of bone metastasis. All patients underwent scintigraphic scan. The result of each scintigraphic scan included an image of the patient in three different color palettes. Thus, the dataset contained 195 images. Images were classified into 4 classes according to the extent of the lesion (Class 1 — no metastases, Class 4 — severe spread of metastases).

The aim of the proposed work is to identify neural networks that would best classify the stages of metastasis bones after training on such a limited dataset.

Taking into account all of the above, neural networks were trained and the following outcomes were obtained.

The prediction of the class, which was images of patients with the smallest of lesion grades (Class 1), was well done by Resnet50 (Rated True Positive (RTP) and Rated True Negative (RTN) values were 1 and 0.87, respectively). However, the highest RTN for Class 1 was equal to 1 and was demonstrated by DeIT. ViT showed moderate values for these parameters — 0.6 for RTP and 0.94 for RTN. However, ViT was the best in determining the second class (RTP = 1, RTN = 0.89). With the definition of the third class, both transformers did well — DeIT had values 0.79 for RTP and 0.92 for RTN, and ViT had 0.79 for RTP and 1 for RTN. Both transformers also distinguished themselves by the perfect definition of the fourth class, with values of 1 for RTP and RTN. The universal F1 score metric was good enough for ViT (0.87), moderate for DeIT (0.78), and very low for ResNet50 (0.57).

Thus, we can conclude that such new perspective neural networks for image classification problems as ViT and DeiT can have good metrics even after training on a limited data set.

DIGITAL PLANTOGRAPHY IN THE STUDY OF THE FOOT IN PREGNANT WOMEN

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Morphological changes during pregnancy significantly alter women's quality of life. Increasing physiological load in the second and third trimesters leads to changes in different parameters of the foot, and adds pressure on its sole surface. The present study is aimed to detect the dynamics of anatomical parameters of the foot of women aged 17-27 in the second and third trimesters during the first pregnancy.

The study was voluntarily attended by 50 women aged 17-27 without musculoskeletal pathology, during the first pregnancy in the second and third trimester. By applying the method of digital planography with graphoanalytic decryption of foot image and system analysis, anatomical parameters of women 's foot in the second and third trimesters of the first pregnancy in dynamics were obtained. Changes in the reference (by changing the parameters of the surface of the whole foot and its three divisions) and spring (K coefficient, Streitter indices, Weisflog indices) functions of the foot were studied. Linear (length, width, height) and angular (angles of I and V fingers and heel angle) foot parameters were obtained.

Digital planography revealed changes in the anatomical parameters of the foot of women aged 17-27 in the second and third trimesters of the first pregnancy. The obtained morphometric information will help to detect in a timely manner the occurrence of longitudinal and transverse flatness at different terms of pregnancy and ensure the choice of the correct conservative or operational treatment, design and manufacture of corrective orthosis, which will significantly improve the quality of life of pregnant women.

MACHINE LEARNING AND INTEGRATIVE ANALYSIS OF OMICS DATA TO SEARCH FOR DIAGNOSTIC SIGNATURES AND THERAPEUTIC TARGETS

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The existing anticancer target drugs do not cover the entire spectrum of malignant neoplasms and their subtypes. Search for new targets is an imortant task. In this paper, the recognition of potential target genes by machine learning is performed.

Using multiomics data from TCGA and CPTAC projects and clinical data from ClinicalTrials and drugbank, we construct a gene classifier that is able to separate the target genes of known anticancer and other drugs. Mutational, transcriptomic, proteomic, methylomic and posttranslational profiles of 8734 patients for 19 types of tumors were used. The features were quantitative values calculated for each gene and type of molecular data at three levels: an individual gene, the gene environment in human interactome, relevant classical molecular pathways. Using the variant of the classifier with the best parameters, the full gene list was annotated, 87 genes were classified as potential oncotargets.

This approach is applicable not only for the search for new target genes, but also for the personalization of patient therapy in the case of training on samples of patients with resistance and sensitivity to the drug. Then, based on the individual multiomics profile of the patient, potentially effective targets may be selected.

СОЗДАНИЕ ЦИФРОВОЙ БАЗЫ ДАННЫХ С АННОТАЦИЯМИ ДЛЯ МУЗЕЯ УЧЕБНЫХ МАКРОПРЕПАРАТОВ

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Актуальность. В настоящее время музей учебных макропрепаратов Института клинической морфологии и цифровой патологии Сеченовского университета насчитывает несколько тысяч уникальных экспонатов, многим из которых более одного столетия. В дополнение к стремительно развивающейся цифровизации процесса изучения макро-и микропрепаратов нами была предложена идея создания обновленной цифровой базы данных макропрепаратов музея с краткой описательной информацией по каждому из них.

Цели и задачи. Целью проекта является создание цифровой базы данных макропрепаратов с размещением информации по ним в открытом телеграм-канале. Каждый макропрепарат будет занесен в цифровую базу данных, а посредством сканирования уникального qr кода обучающиеся смогут перейти в тг-канал на пост фотоснимка макропрепарата с условными обозначениями, подписями, описанием и характеристикой патологического процесса, в нём отображённого.

Задачами проекта являются:

1. Непосредственное создание источника информации (телеграм-канала)
2. Набор инициативной группы (сотрудники, обучающиеся)
3. Подготовка информации по каждому учебному макропрепарату
4. Публикация данной информации
5. Создание QR-кодов, содержащих ссылку на нужную публикацию

Ожидаемые результаты. Среди ожидаемых результатов планируется отметить рост заинтересованности обучающихся в изучении патологической анатомии, повышение доступности учебных макропрепаратов, и, как следствие, повышение показателей средней успеваемости на экзаменах.

Выводы. Институт клинической морфологии и цифровой патологии активно работает над цифровизацией как клинических, так и педагогических задач, и данный проект может стать весьма успешным дополнением к уже имеющимся интерактивным базам данных, атласам патологической анатомии, что будет положительным образом сказываться на комплексности развития цифровизации на базе Института.

LASERS

RAMAN FLUORESCENCE SPECTROSCOPY: APPLICATIONS IN DIAGNOSTICS OF PROSTATE CANCER

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Raman fluorescence spectroscopy allows minimally invasive real-time detection of prostate pathologies. To characterize pathologic lesions, we developed a model Raman-fluorescence microscopic system using fluorescence and Raman scattering. Simultaneous visualization of fluorescence and Raman signals in the InVivo mode is possible with the use of a fiber optic bundle built into an endoscopic tube or aspirating needle for pre- and intraoperative diagnostics. **Objective:** to evaluate the ability of Raman fluorescence spectroscopy (RFS) to detect benign prostatic hyperplasia (BPH) and prostate cancer.

Materials and Methods: We analyzed preoperative results of RFS examination of prostate tissue samples from 62 patients, who later underwent radical prostatectomy. The spectra correlated with the histological features and were used to develop diagnostic algorithms. These algorithms were tested to verify their ability to find pathologic regions using a Raman-fluorescence spectrum. The results were analyzed in accordance with the Gleason grading system and PSA levels.

Result: It was established that there is a direct relation between fluorescence intensity and Gleason score. Important distinctions between the spectra of BPH and prostatic cancer were found in regions with specific vibrations of glycogen molecules, phospholipids, carotenoids and NADH. **Conclusion:** The results of the investigation showed that Raman fluorescence spectroscopy can be used as an accurate and early method of prostate cancer detection. Being safe and inexpensive, RFS is used on-line and takes only several minutes. It enables to interactively identify tumorous regions pre- and intraoperative and define the volume of surgical intervention with maximum precision.

OPTICAL AND LIQUID BIOPSY OF PATIENTS WITH CANCER, CHRONIC KIDNEY DISEASES AND HEART FAILURE

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Introduction. In modern world practice, promising diagnostic methods are emerging, such as “optical biopsy” and “liquid biopsy”, which are used for specific diseases biomarkers detection in biological tissues and fluids. Optical methods have the potential to overcome the limitations of traditional methods of clinical analysis. One of the most promising methods of optical analysis (and optical biopsy) is a Raman spectroscopy, which can contribute to understanding of molecular basis of diseases and creation of new bioanalytical tools for the diagnosis of diseases. Since each type of biological tissue and biofluid has an individual molecular composition and, thus, a unique spectral profile resulting from the transition of a molecule from one vibrational-rotational state to another, a set of such individual states of functional groups of nucleic acids, proteins, lipids and carbohydrates makes it possible to characterize component composition of tissues, which ultimately makes it possible to isolate disease markers.

Along with the use of optical biopsy methods, it is possible to apply a supersensitive technique for analyzing biofluids based on surface-enhanced Raman spectroscopy, which will be most effective for detecting low concentrations of disease markers in biological fluids. In the last decade, the development of nanotechnology has led to the creation of promising tools for solving new problems in the study of various human diseases, which is especially important for effective and targeted treatment and a deeper fundamental understanding of the biochemistry of diseases.

In this study we demonstrate application of conventional Raman spectroscopy for the analysis of skin and application of SERS for serum analysis to determine the presence of kidney and heart diseases.

Methods. The study of skin optical biopsy of skin cancer patients was performed for more than 600 patients of Samara Oncological Regional Clinical Dispensary. The study of skin optical biopsy was performed for three groups of subjects: the target group consisting of 85 hemodialysis patients with kidney failure (90 spectra series), the adult control group constituted by 40 healthy volunteers (80 spectra) without systemic diseases and the young control group constituted by 84 healthy volunteers (168 spectra) without systemic diseases. Stimulation of the collected spectra was performed by the laser module (LuxxMaster LML-785.0RB-04, PD-LD, New Jersey) with the central wavelength of 785 nm. The Raman probe (RPB785, InPhotonics, Massachusetts) is able to focus the exciting radiation, as well as to collect and filter the scattered radiation. The focal length of the utilized Raman probe was 7.5 mm with the distance between the tested skin sample and the output lens of the Raman probe of 7 mm. The collected signal was decomposed into a spectrum using a portable spectrometer (QE65Pro, Ocean optics, Florida).

In SERS analysis of blood the collected samples were placed in sterile tubes. Between sampling and direct recording of spectral characteristics, the samples were stored at -14 ° C. The experimental setup for blood liquid biopsy includes a spectrometric system (EnSpectr R785, Spektr-M, Chernogolovka, Russia) and a microscope (ADF U300, ADF, China). Focusing the exciting radiation and collecting the scattered radiation were implemented using 50x Objective LMPlan. The stimulation of collected spectra was performed by the laser module with central wavelength 785 nm. A yellow-green sol with a silver concentration of 0.05-0.1 g/l was obtained by reduction from an aqueous solution of silver nitrate with sodium citrate at a temperature of 95 ° C for 10 minutes. For SERS testing, a 1/1 silver colloid is added to the serum sample. Initial serum samples and samples of serum solutions with silver sol in a volume of 6 µl are applied to aluminum foil and dried for 60 minutes at room temperature.

In this study, the in vitro analysis of human serum was performed for 205 subjects, including 69 healthy subjects and 61 patients with chronic heart failure (CHF). Analyzed groups separation based on deep learning was implemented using a separate one-dimensional convolutional neural network (CNN). The choice of the CNN architecture for recognition of the current SERS dataset consisted of several consecutive stages. At the first stage, the verified CNN configurations and advanced deep learning practices based on CNN were examined. Analysis of the work by other research teams has shown that the following CNN configurations are characterized by their possible abilities to recognize Raman spectra: sequential CNNs, CNNs containing the Inception module, CNNs with residual connections, ensemble CNNs, CNNs based on a combination of convolutional layers with recurrent layers.

Results and discussion. The achieved accuracy in ROC AUC for CNN is significant ($p<0.01$) in comparison to the PLS implementation for all the three analyzed tasks for skin cancer (benign vs malignant; melanoma vs pigmented lesions; melanoma vs seborrheic keratosis). For discriminating Malignant and Benign neoplasms, the achieved ROC AUC with CNN implementation is as high as 0.96 (0.94 — 0.97; 95% CI). For the two other dichotomy classification tasks, the ROC AUCs are slightly lower. Figure 1 demonstrates the achieved ROC curves for CNN discrimination between Malignant and Benign tumors as well as the ROC curves obtained in different studies and the accuracies provided by medical specialists. The presented results show that CNN-based analysis of noisy Raman spectra can produce ROC AUCs that outperform or at least equal to the results provided by medical specialists. Moreover, the proposed CNN analysis of the Raman spectral data even outperforms the approaches based on CNN analysis of skin tumor images. In the study by Haenssle *et al.*, the CNN algorithm classified 60 cases of benign lesions (30 NE, 10 SK, 10 solar lentigo, 5 angiomas, 5 dermatofibromas) vs 40 cases of malignant and premalignnat lesions (15 MM, 10 BCC, 5 SCC, 5 actinic keratosis, 5 Bowen's disease). All 100 cases included pigmented/non-pigmented and melanocytic/non-melanocytic skin lesions. The CNN approach for tumor image analysis revealed a sensitivity, specificity, and ROC AUC of 95% (84 — 99%; 95% CI), 77% (65 — 86%; 95% CI), and 0.92 (0.87 — 0.97; 95% CI). In addition, the study by Haenssle *et al.* provided the results of skin tumors classification provided by 96 trained dermatologists with different experience (beginner, skilled, expert). Dermatologists were asked to indicate their dichotomous diagnosis (malignant/premalignant, benign) on the basis of dermatoscopic image of the lesion. The dermatologists' mean sensitivity of 89% (87 — 91%; 95% CI) and specificity of 81% (79 — 83%; 95% CI) are presented in Figure 1.

Application of Raman spectroscopy to investigate the forearm skin has yielded the accuracy of 0.96, sensitivity of 0.94 and specificity of 0.99 in terms of identifying the target subjects with kidney failure. The autofluorescence analysis in the near infrared region identified the patients with kidney failure among healthy volunteers of the same age group with specificity, sensitivity, and accuracy of 0.91, 0.84, and 0.88, respectively. When classifying subjects by the presence of kidney failure using the PLS-DA method, the most informative Raman spectral bands are 1315 to 1330, 1450 to 1460, 1700 to 1800 cm^{-1}. In general, the performed study demonstrates that for *in vivo* skin analysis, the conventional Raman spectroscopy can provide the basis for cost-effective and accurate detection of kidney failure and associated metabolic changes in the skin.

The results of the SERS data for CHF demonstrates that CNN significantly outperforms standard methods of analysis as projection on latent structures and allows for detection of CHF with 95-100% accuracy. By means of multivariate analysis, the informative spectral bands associated with the CHF during disease progression were identified. In addition, the analysis of the correlation between the serum spectral characteristics and urea, creatinine

has made it possible to determine the spectral bands correlated with levels of creatinine and urea into the complex spectral characteristics of serum. In general, the reported approach may form the basis for monitoring the health status of CHF patients and find application in studying other pathological conditions of the human body.

Conclusion. Raman-based optical and liquid biopsy may be promising in non-communicable diseases identification, as it provides fast and rapid diagnosis.

This study was supported by Russian Science Foundation grant No. 21-75-10097.

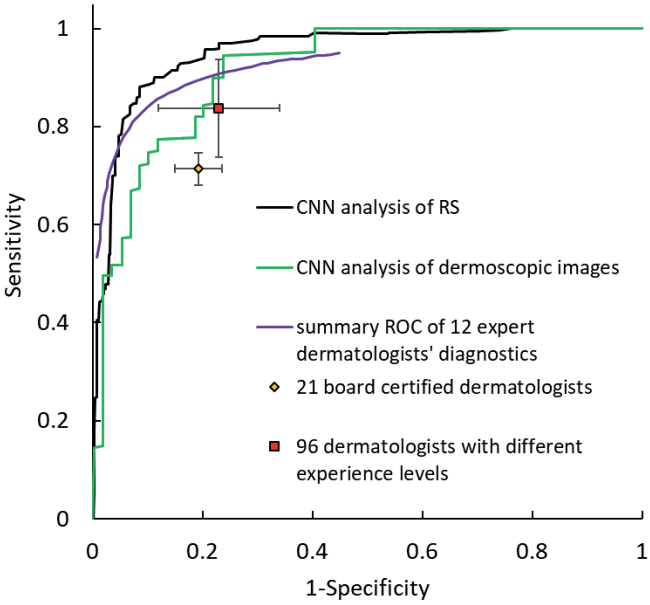

Figure 1. The ROC curves and diagnostics performance of different medical specialists and proposed CNN analysis of Raman spectra (RS) with ROC AUC of 0.96 (0.94 — 0.97; 95% CI); CNN analysis of dermoscopic images to classify 60 cases of benign lesions vs 40 cases of malignant and premalignant lesions with ROC AUC of 0.918 (95% CI 0.866–0.970); summary ROC of 12 expert dermatologists' diagnostics presented in a *Cochrane review*. The diagnostics performance of 21 board certified dermatologists to classify 71 malignant vs 40 benign lesions. The diagnostic performance of 96 dermatologists with different experience levels: 17 beginners (<2 years of experience), 29 skilled (2 — 5 years of experience), and 40 experts (>5 years of experience).

NEW OPTICAL SCREENING TOOL FOR DETECTION OF PERIPHERAL ARTERIAL DISEASE IN PATIENTS WITH DIABETES MELLITUS

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Objective. The aim of the study was to evaluate the the sensitivity and specificity of a new method for assessing foot tissue perfusion (Incoherent optical fluctuation flowmetry method (IOFF)) in the diagnosis of peripheral artery disease (PAD) in patients with diabetes mellitus (DM).

Methods. A total of 54 patients with type 2 DM were included in the study; study was carried out on 108 feet. According to ultrasound duplex scanning, hemodynamically significant stenoses of the main arteries were diagnosed in 39 lower extremities, and there were no hemodynamically significant stenoses in 69 lower extremities. The foot tissue perfusion was measured in perfusion units (PU) using the new IOFF method during a local heating test on the dorsal surface of the foot. The time duration of the test was 6 minutes.

Results. It was shown that the IOFF method with a sensitivity of 79,5% and a specificity of 88,4% allows to detect limbs with hemodynamically significant stenoses (AUROC 0.884, CI: 0.817-0.953).

Conclusion. The IOFF method is promising as a noninvasive, accessible, rapid screening tool for detection of PAD in patients with DM.

SERS APTASENSORS FOR ULTRASENSITIVE DETECTION OF VIRUSES IN BIOLOGICAL FLUIDS

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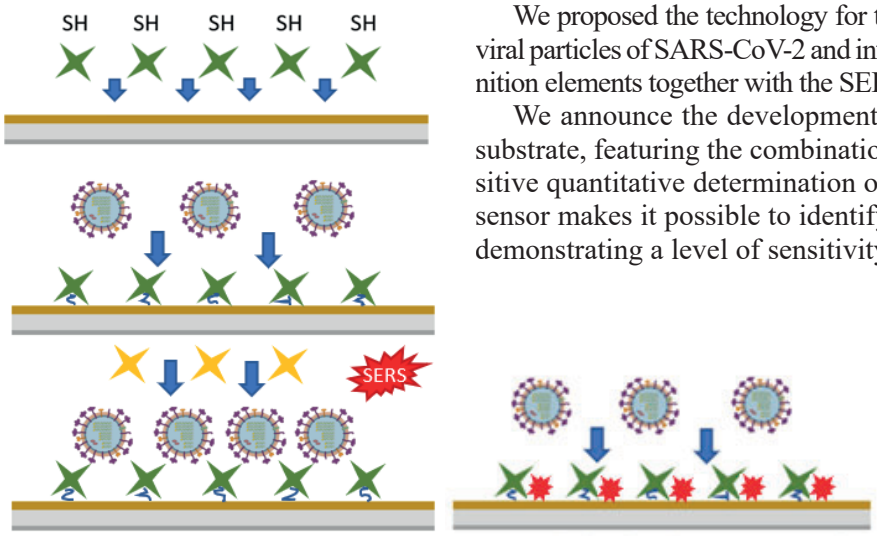

We proposed the technology for the rapid and sensitive detection of the whole viral particles of SARS-CoV-2 and influenza viruses using DNA aptamers as recognition elements together with the SERS method for detecting the optical response.

We announce the development of a SERS-aptasensors based on a SERS substrate, featuring the combination of high speed, specificity, and hypersensitive quantitative determination of SARS-CoV-2 and influenza viruses. The sensor makes it possible to identify virus virions in very low concentrations, demonstrating a level of sensitivity comparable to the existing gold standard of diagnostics — polymerase chain reaction with reverse transcription.

Figure. Schematic representation of two types of aptasensors

LASER FORMATION OF THREE-DIMENSIONAL BIOSCAFFOLDS TO CREATE A LUNG PHANTOM FOR RESEARCH

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The main causes of death in the world can be roughly divided into three groups: cardiovascular diseases, respiratory diseases and neonatal pathological conditions. Lung transplantation is the main intervention for end-stage lung disease, but due to the lack of donor organs and the low survival rate of patients after lung transplantation (30% chance of a patient surviving for 10 years after surgery), alternative approaches are being sought to solve this problem. One such approach is the complete or partial replacement of lung tissue using tissue engineering. Of particular interest to scientists is the development of models that mimic the qualities and properties of real lungs for in vitro studies, called phantoms. One of these models is bioconstructions for studying the mechanism of the course of respiratory diseases, on which lung cells can be grown. The purpose of our study is to analyze the relevant literature on this topic, to consider existing methods, in order to select the most optimal methods and materials for creating a lung phantom on their basis.

Bioconstructions can have completely different morphology, but at the same time, morphology does not have as much influence as it does, first of all, the compatibility of the material itself with cells, surface roughness/porosity. Conventionally, materials for the manufacture of scaffolds can be divided into two groups: synthetic and natural. Natural polymers have additional advantages such as bioresorbability and antiseptic properties. Meanwhile, synthetic polymers are better suited to provide strength and resilience. The most common biomaterials for creating a lung phantom are elastin, fibrin, collagen, chitosan, and gelatin. Among synthetic materials, polyethylene glycol (PEG) and polysiloxane (silicone) are considered relatively safe for growing cells, an elastic polymer that is widely used in clinical practice due to its low toxicity and high mechanical strength. However, mentioning the morphology, it is worth noting that the control of the substrate topography, substrate rigidity, mechanical forces, and density makes it possible to increase the accuracy of further studies with cells grown on these constructs. It is also worth noting that 3D bioconstructs have more advantages than 2D bioconstructs, as cells in a 2D environment are not exposed to the same conditions as cells in 3D body tissues.

Most bioconstructions are created by bioprinting methods, as one of the main advantages of bioprinting over other fabrication methods is the ability to print complex patterns in larger geometries from biological hydrogels seeded with cells surrounding a strong polymer structure. The printing technology used can also play a role in cell selection. Techniques such as extrusion printing can damage cells when shear forces are applied during the printing process, while laser printing exhibits the highest degree of cell viability. Recent technological innovations related to bioprinting technologies have led to the development of 2-photon polymerization, a laser-assisted bioprinting technique with resolution in the nanometer range. However, selective laser sintering is a more versatile and affordable method of laser printing, which makes it possible to form porous structures for subsequent cell colonization. This method is based on layer-by-layer sintering of a fine powder in accordance with a given 3D model. Also, in our studies, the method of forming a composite by laser radiation in the visible and infrared wavelengths of light was often used.

As radiation sources, we used a Nd:YAG laser with a wavelength of 532 nm and a duration of 16 ns and a titanium-sapphire femtosecond laser (Ti:Sa) operating at a wavelength of 810 nm with a pulse duration of 140 fs and a frequency of 80 MHz. Liquid dispersed media were combined with single-walled and multi-walled carbon tubes (CNTs), since their addition to natural or synthetic polymer structures improved mechanical properties, and due to their ability to absorb radiation, drying of bioconstructions with a laser generally occurred more evenly than without them.

In a further experiment, based on the analysis of the literature, it is planned to create a porous structure from gelatin and sodium chloride by combining the leaching method and the method of forming a composite by radiation with the addition of SWCNTs.

THE ASSESSMENT OF THE RESULTS OF THE BIOLOGICAL RESPONSE OF THE ORAL MUCOSA ON THE EFFECT OF LASER IRRADIATION WITH A WAVELENGTH OF 445±40 nm

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The scientific and technological union “IRE-Polyus” (Russia) created an experimental diode laser with a wavelength of 445±40 nm. This laser technology is declared as a contactless surgical device, which involves minimally invasive surgical manipulations. The introduction of the blue laser technology in dentistry causes the importance and need to conduct research on the study of the biological response of a living organism on the effect of laser irradiation with a specified wavelength. In this experimental study, the object of study was 24 mature laboratory male rats (WISTAR). The linear section of the oral mucosa was carried out using a blue laser with a contactless way with a laser irradiation power — 0,7W with constant mode (CW) and inexhaustible fiber with a diameter of 400 μm. The determination of temperature was measured with DT–1200 digital thermometer (IzTekh LLC, Russia). A biopsy of the mucous membrane was performed, 2 mm from all sides. Histological analysis was performed by the method of light pouring light microscopy using the Leica DM 4000B LED (Germany) microscope. Statistics was carried out using the program R v.4.1. When forming a cut of the oral mucosa with laser wavelength 445±40 nm, the non contact method in the surgical field did not exceed 59°C. The average value was 52,4±4,2°C, which indicates a slight thermal effect on the tissue. The histological analysis detected small-scale foci of coagulation necrosis and no signs of inflammatory infiltration. The results indicate the safety of irradiation of the blue laser and allow planning clinical studies.

OPTICAL SPECTROMETRY OF ENDOMETRIUM AS AN INNOVATION METHOD OF IVF OUTCOMES PREDICITON

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The ability of accurate prediction of pregnancy chances and adverse pregnancy outcome risks is the difficult deal. At the same time it is extremely important task in gynecology and obstetrics nowadays. One of the important criteria is an assessment of local and general oxygenation level. We evaluate efficiency of endometrium and oxygenation levels as the predictor of pregnancy outcome in IVF programs.

The optical spectrometry was used in 160 patients aged 36-48 years (42 ± 1.3).

The positive pregnancy test was detected in 23 (14.4%) women. In the pregnant group the endometrium oxygenation level was 74 ± 1.2 units. The negative pregnancy test results were observed in 137 (85,6%) patients. The range of endometrium oxygenation level in this group was 22 ± 1.4 units. The biochemical pregnancy (early pregnancy loss) was diagnosed in five cases. In this group, we observed the decreasing skin level of oxyhemoglobin after 7-11 days to 29 ± 0.7 units.

Thus, the evaluation oxyhemoglobin levels in endometrium could be considered as important prediction marker of the successful implantation and favorable pregnancy outcomes.

НОВЫЙ СПОСОБ РЕПАРАЦИИ КОСТНОЙ ТКАНИ С ИСПОЛЬЗОВАНИЕМ ЛАЗЕРНОГО ОБЛУЧЕНИЯ

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Актуальность: Поиск путей влияния на репаративный остеогенез рассматривается как одна из актуальных проблем биологии и медицины. Решение ее возможно, в частности, посредством использования различных аллогенных материалов, позволяющих поддерживать и стимулировать процесс естественного течения репаративной регенерации [1, 2, 3].

Коллаген и хитин с его производной хитозаном являются одними из наиболее важных для живых систем биополимеров. Коллаген составляет основу костных и мягких тканей млекопитающих (в том числе и человека), а из хитина и хитозана построены силовые элементы насекомых, крабов, грибов. Поэтому исследования свойств этих веществ, их комбинаций и изменений структуры под воздействием экзогенных факторов важны при разработке новых методов репарации костной ткани при травматическом повреждении [1, 4].

Цель исследования: разработать новый метод репарации костной ткани при травматическом повреждении с использованием коллаген-хитозанового комплекса с воздействием лазерного облучения.

Материалы и методы: Исходными материалами являлись коллаген (V), хитозан, дистиллированная вода. Из исходных материалов готовили композиции в равных соотношениях коллагена и хитина с использованием механического растворения в дистиллированной воде до образования губчатого материала, визуально напоминающего структуру костной ткани (далее — суспензия). Полученный гель наносили на предметное стекло оптического микроскопа модель (Carl Zeiss Jena Amplival). Лазерное воздействие проводилось облучением геля непосредственно на предметном столике микроскопа полупроводниковыми лазерами с различными спектрами цветового излучения (синий, красный и зеленый) с интенсивностью порядка 1 вт/см^2. С помощью микроскопа и видеокамеры проводили регистрацию изображения образцов в проходящем и отраженном свете, поляризованном и неполяризованном, и их изменения в процессе лазерного воздействия. Была проведена 3-х кратная серия экспериментов с отдельными веществами и композицией.

Результаты: Исходные водные композиции коллагена и хитозана в поляризованном свете имели различную структуру. Суспензия в скрещенных поляризаторах не визуализировалась, в то время как частицы хитозана определялись, как пятна повышенной яркости. Таким образом, суспензия в исходном состоянии оптически изотропна, в то время как хитозан демонстрирует выраженную оптическую анизотропию, поскольку отдельные частицы хитозана уже в исходном состоянии имеют выраженное кристаллическое упорядочение. При воздействии на опытную суспензию лазером различного цветового спектра было выявлено формирование оптически анизотропных зон вначале со стороны воздействия лазера с последующим равномерным распространением на всю площадь опытной суспензии. Выраженные изменения структуры, характеризующиеся равномерной кристаллизацией опытного материала, определяемой в поляризованном свете, были выявлены на вторые сутки после экспозиции в темном месте при свободном доступе воздуха. *В ходе дифрактометрии, проведенной через 1 месяц, было выявлено формирование прочной, ориентированной структуры. В контроле опытной суспензии, без воздействия лазерного облучения, признаки прочной ориентированной структуры не выявлены.* При сравнении результатов кристаллизации под воздействием лазерного излучения различного цветового спектра было выявлено, что наилучшим эффектом обладал лазер зеленого цвета, характеризующийся более равномерным и структурированным формированием анизотропных зон.

Выводы: Композиция коллагена и хитозана с последующим воздействием лазерного облучения зеленого цветового спектра является перспективным материалом для репарации костной ткани.

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MASS-SPECTROMETRY IN MEDICINE

CHARACTERISTICS OF PNEUMOCYSTOSIS IN CHILDREN WITH RECURRENT RESPIRATORY INFECTIONS

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Introduction: Pneumocystis jirovecii is an opportunistic fungal pathogen that can cause pneumocystosis in immunocompromised people. Risk factors for pneumocystosis include conditions that lead to cell-mediated immunodeficiency. The treatment efficacy of this disease mainly increases with early recognition, in clinical stages that do not have pronounced forms of the course. The use of a systematic approach implemented in personalized medicine can significantly increase the treatment efficacy. At the present stage, personalized medicine is commonly referred to as 5P medicine. It includes Personalized, Preventive, Participative, Predictive and Pluri-expert.

To calculate the criteria for assessing the state of health in the framework of personalized medicine, it is advisable to use multivariate statistics and mathematical modeling, since the concentrations of indicators depend on many multidirectional processes and represent noisy data. So factor analysis and linear discriminant analysis are recognized as the most effective methods. Linear discriminant analysis is used for identification of the unique ratio of the concentrations of indicators of the disease under study.

Aim: This study aims to calculate of the unique ratio of microbial markers of blood samples obtained by GC-MS in pneumocystosis using linear discriminant analysis (LDA).

Materials and methods: 126 patients aged 7-13 years were examined at the children's clinical sanatorium: 25 patients with pneumocystosis were included in the primary group, 101 — in the comparison group. Blood samples from patients with recurrent respiratory infections were performed using a MAESTRO 7820A chromatograph combined with an Agilent Technologies selective mass spectrometer. At the time of sampling, patients had no clinical manifestations. Statistical analysis and mathematical modeling were carried out using linear discriminant analysis in the Statistica 8.0 program.

Results: Modeling of indicators obtained by GC-MS was carried out in several stages. Stage 1 consisted in the selection of indicators for inclusion in the model. At the 2nd stage, a mathematical model of the first step was built. After comparing the values, a contingency analysis identified a candidate indicator for exclusion from the model. As a result of iterations with a step-by-step elimination of components, 6 components were included, corresponding to the parameters of the specified accuracy of the model. Components included in the model: concentrations of isomyristic aldehyde, cycloheptadecanoic acid, 7,8-hexadecenoic acid, cis-vaccenic acid, myristic aldehyde, iso-palmitic acid. The greatest discriminating function was noted for the concentration of the indicator myristic aldehyde. The resulting classification equation makes it possible to determine pneumocystosis with a predictive accuracy of 89%, a specificity of 97%, and a sensitivity of 44.4%. For each patient, the uniqueness coefficient was calculated from the coordinates of the centroids for the discriminant function. The uniqueness coefficient allows to quantify the clarity of the metabolomic imprint of pneumocystosis.

Conclusion: The resulting classification equation allows screening diagnostics of pneumocystosis according to the results of blood chromatography-mass spectrometry. Thus, the results of studying the condition of patients with immune-mediated diseases make it possible to identify the risk of pneumocystosis in children with recurrent respiratory infections. This helps to increase the treatment efficacy, subject to the patient's request for a more detailed examination.

GC-MS ANALYSIS OF CHEMICAL COMPOSITION OF NEW MEDICINE ON THE BASE OF CORTEX QUERCUS EXTRACT FOR PREVENTION OF PERIODONTAL DISEASES

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The use of GC-MS analysis based on the method of the equilibrium vapor-gas phase for studying the chemical composition of the main groups of biologically active substances (BAS) of the new medicine on the base of ethanol extract of the oak cortex is proposed. The 26 chemical compounds were identified reliably; the method allows

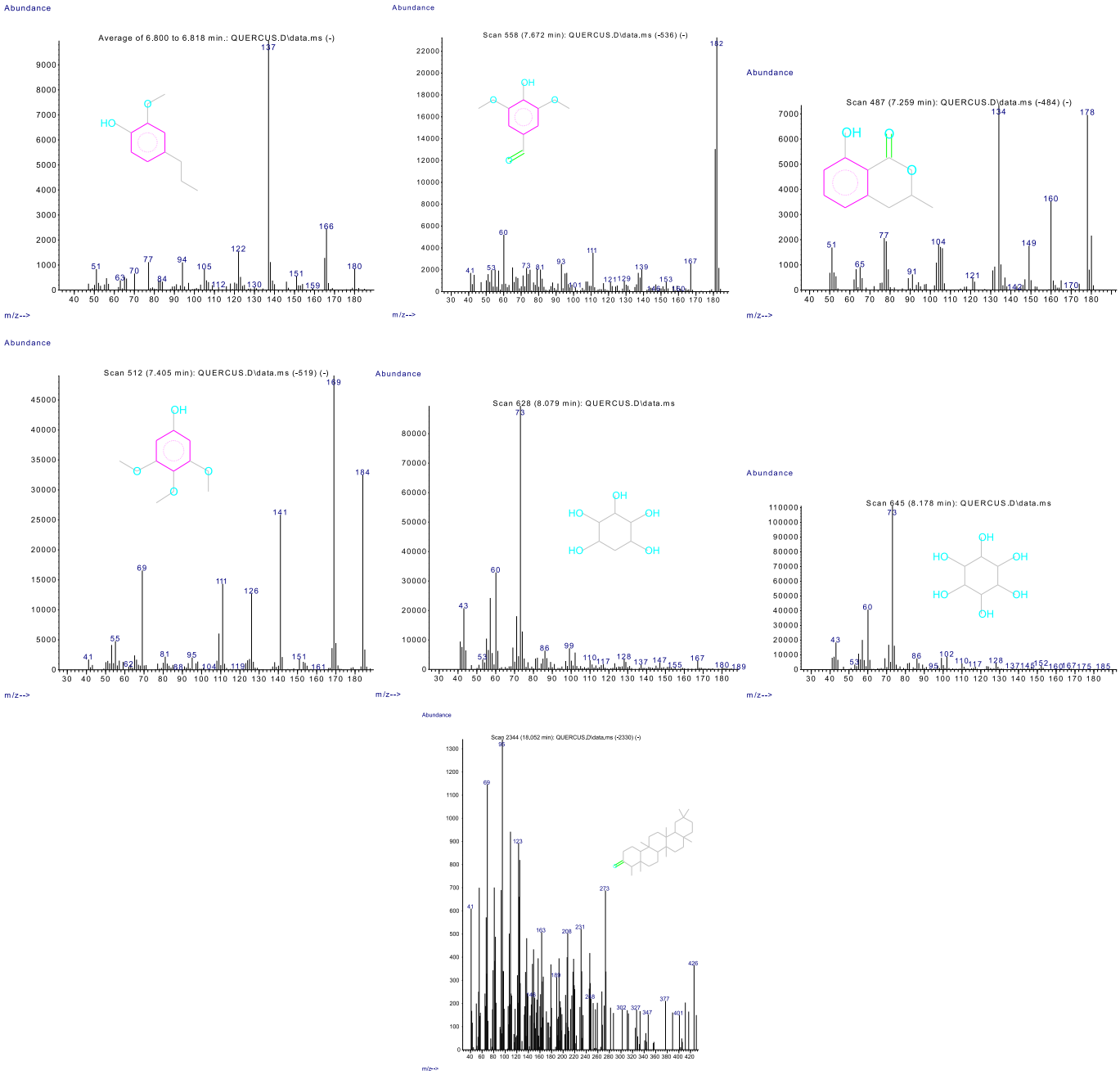

Figure 1. Mass spectra of the main BAS of the new medicine on the base of oak cortex ethanol extract: (1) 2-methoxy-4-propylphenol, (2) syringaldehyde, (3) mellein, (4) antiarol, (5) 1-deoxyinositol, (6) scyllo-inositol, and (7) friedelin

analysis without special sample preparation. The content of levoglucosan, antiarol, 1-deoxyinositol, scyllo-inositol, squalene, *gamma*-sitosterol, sitostenone, palmitic, stearic, palmitoleic and linoleic acids was determined.

The typical chemical compounds for identification of major BAS groups are 2-methoxy-4-propylphenol, syringaldehyde, mellein, antiarol, 1-deoxyinositol, scyllo-inositol, and friedelin (Fig.1). The results of the GC-MS analysis can serve to optimize the analysis of the quality of multicomponent herbal medicines based on water-ethanol extracts from the oak cortex. The results can also be used in the case of the additional objectification of the quality evaluation of the above medicines when carrying out the studies in conjunction with pharmacopoeial methods.

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DE NOVO СЕКВЕНИРОВАНИЕ ЭНДОГЕННЫХ БИОЛОГИЧЕСКИ АКТИВНЫХ ПЕПТИДОВ

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В основе многих современных лекарственных препаратов лежат природные соединения, обладающие биологической активностью. К ним относятся, в частности, пептидные токсины и антибиотики, а также антимикробные пептиды. Первым шагом при изучении таких пептидов является установление их первичной структуры. Так как интерес представляют, прежде всего, неизвестные ранее соединения, для этих целей необходимо использовать методы *de novo* секвенирования.

За последние двадцать пять лет был разработан целый ряд алгоритмов и компьютерных программ для *de novo* секвенирования пептидов. Однако практически все существующие подходы ориентированы на обработку данных масс-спектрометрии «снизу-вверх» (bottom-up) и подразумевают, что исследуемые пептиды были получены путем гидролиза анализируемых белков с использованием ферментов определенной специфичности. Очевидно, подобные предположения неприменимы к эндогенным биологически активным пептидам.

В докладе будут обсуждаться подходы к изучению таких пептидов, в основе которых лежит алгоритм Twister для *de novo* секвенирования белков и пептидов по данным масс-спектрометрии высокого разрешения (Vyatkina et al, 2015, 2016, 2017, 2022). Будут приведены результаты, полученные для ядов черной и зеленой мамбы (*Dendroaspis polylepis* и *Dendroaspis viridis*) и кожного секретома лягушек (*Rana arvalis* и *Rana temporaria*), которые подтверждают эффективность предложенных методов, и обозначены направления для дальнейшего их усовершенствования.

КОЛИЧЕСТВЕННАЯ ПРОТЕОМИКА НА ОСНОВЕ МАСС-СПЕКТРОМЕТРИИ ВЫСОКОГО РАЗРЕШЕНИЯ В ЗАДАЧАХ ПОИСКА МИШЕНЕЙ И МЕХАНИЗМОВ ДЕЙСТВИЯ ОНКОПРЕПАРАТОВ

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Выяснение механизмов жизнедеятельности клеток и их развития, включая изменения в результате лекарственного воздействия, влияния внешних факторов или физиологического состояния самого организма, является одной из основных задач современных постгеномных исследований и разработок в области «омиксных» технологий и системной биологии. Современные высокопроизводительные методы масс-спектрального анализа, появившиеся в последние годы, существенно расширили возможности для выявления качественных и количественных изменений протеомов клеток в результате лекарственного воздействия, влияния внешних факторов или физиологического состояния самого организма. Более того, в настоящее время появились возможности выявлять такие изменения на уровне всего клеточного протеома и, соответственно, идентифицировать более широкий, чем ранее предполагалось, спектр воздействия лекарств на белки клеток, а также активируемых каскадов белок-белковых взаимодействий. Так, например, при воздействии химиотерапевтического препарата на раковые клетки, его мишенями могут быть не только «титульные» для данного лекарства, но и другие белки протеома, которые могут запускать ранее неизвестные механизмы действия, с которыми могут быть связаны как побочные эффекты терапии, так и возможные механизмы выработки резистентности. Одним из основных подходов в подобных исследованиях является качественный и количественный анализ ассоциированной экспрессии белков протеомов. Возможности метода будут продемонстри-

рованы на примере анализа количественных полнопротеомных данных, полученных ранее для большой выборки химиотерапевтических препаратов, используемых в клинической практике или находящихся в стадии экспериментальной терапии. В докладе также будут рассмотрены биоинформатические подходы к обработке хроматомасс-спектрометрических данных экспрессионной протеомики, позволяющие выявлять сигнатуры как известных внутриклеточных процессов, ассоциированных с лекарственным воздействием, так и неизвестных ранее механизмов действия ряда лекарств.

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МЕТАБОЛОМИКА В МЕДИЦИНЕ

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Введение: Метаболомика активно позиционирует себя в современной медицине, как еще одна омиксная технология с потенциалом широкого развития в области превентивной диагностики мультифакториальных заболеваний. Используя широкий арсенал технологических и биоинформитических подходов, формируются панели метаболомных маркеров, характеризующих различные патологические состояния. При этом в равной степени метаболомика решает как фундаментальные, так и прикладные задачи в современной медицине. Отмечены успехи по составлению панелей маркеров для диагностических задач кардиологии, онкологии, гинекологии и других медицинских направлений. В данной работе продемонстрирован всесторонний подход к поиску метаболомных биомаркеров для воспалительных заболеваний кишечника (ВЗК).

Материалы и методы: Сбор образцов с ВЗК был произведен на базе 123 клинической больницы ФГБУ ФНКЦ ФХМ ФМБА России. Болезнь Крона (n=35), Язвенный колит (n=25), Здоровый контроль — (n=50). Поиск биомаркеров осуществлялся в нетаргетном режиме с использованием следующих приборов: SCIEX QTOF 6600 (TripleTOF 6600+ System) и Shimadzu QP2010 Ultra с парофазным экстрактором Shimadzu HS-20.

Результаты: в ходе работы произведен экспериментальный анализ метаболитов и отдельно липидов в биологических образцах пациентов с ВЗК и группы контроля методом ВЭЖХ-МС. В ходе анализа липидов выявлено и идентифицировано 720 соединений, среди которых производные и региомеры таких классов липидов, как: NAE, CER, LPC, DG, SM, LPE, TG, PC, HEX, PI, VAE, PE. Значимые отличия показаны для таких соединений как, Cer37:0;3O| Cer20:0;2O/17:0;O_Unk, PC 40:8|PC 18:2_22:6, PEP-46:7|PEP-24:1_22:6 и HBMP54:8|HBMP16:2_19:2_19:4. В ходе анализа метаболитов выявлено порядка 50 соединений, среди которых значимые отличия были получены для Urocanic Acid, Nicotinamide, Sphingosine, Acetylcarnitine, O-Acetyl-L-carnitine, 5'-S-Methylthioadenosine, Adenine, 3-Hydroxyanthranilic и N-Acetylcytidine. В ходе исследования летучих соединений значимые отличия были продемонстрированы для Butanoic acid, Hexadecanal, Indole, Pentanoic acid, Pentanoic acid 4-methyl-, Phenol и Hydrocinnamic acid.

Выводы: Всестороннее изучение результатов метаболомного анализа приводит к формированию панелей метаболомных маркеров, которые могут быть подвергнуты дальнейшему исследованию в расширенных группах.

МЕТОДЫ ЛАЗЕРНОЙ ИОНИЗАЦИИ В МАСС-СПЕКТРОМЕТРИИ ЛЕТУЧИХ ОРГАНИЧЕСКИХ СОЕДИНЕНИЙ

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Состав летучих органических соединений (ЛОС), выделяемых живыми организмами, несет информацию об их состоянии. Эта информация может быть использована, в том числе, в медицине для диагностики состояния человека. Масс-спектрометрия ЛОС — наиболее информативный метод анализа, однако в силу крайне разнообразного состава ЛОС необходим метод получения ионов, обеспечивающий возможность детектирования соединений вне зависимости от их свойств.

В докладе рассматриваются три метода ионизации ЛОС с использованием импульсного лазерного излучения — лазерная десорбция ионов ЛОС с поверхности наноструктурировнного кремния (SALDI), ионизация ЛОС импульсным излучением лазерной плазмы и лазерная ионизация единичных аэрозольных частиц.

Метод ионизации на наноструктурированной поверхности кремния (SALDI) является наиболее чувствительным методом обнаружения ЛОС. Полученная в настоящее время вероятность ионизации органических молекул достигает 10^{-2} для ряда соединений, что обеспечивает предел обнаружения на уровне 1 ppt. Однако высокая вероятность ионизации реализуется только для соединений с высокой энергией сродства к протону или электрону. Для большинства ЛОС живых организмов этот метод неэффективен. Лазерная плазма, формируемой импульсным излучением на металлической поверхности, создает поток вакуумного УФ излучения, которое может быть использовано для ионизации ЛОС. Спектр излучения лазерной плазмы находится в области вакуумного УФ излучения, энергия кванта которого достаточна для ионизации ЛОС. При ионизации излучением лазерной плазмы в потоке аргона при атмосферном давлении вероятность образования иона для любых соединений достигает 10^{-6} -10^{-7}. В большинстве случаев регистрируемые ионы являются продуктами реакций, в первую очередь реакций передачи протона от иона H_2O^+. Пилотные эксперименты по детектированием ЛОС образцов мочи мышей, зараженных гепатокарциномой и людей с патологией почек показали, что состав ЛОС, определяемый данным методом, может быть индикатором наличия патологии организма [1]. Лазерная масс-спектроскопия одиночных аэрозольных частиц основана на испарении и ионизации частицы импульсным лазерным излучением УФ диапазона. В докладе рассматривается пока нереализованная возможность применения для испарения и ионизации органических частиц многочастотного лазерного воздействия, при котором испарение частицы первым лазером предшествует многочастотному возбуждению и ионизации органических соединений, сорбированных на поверхности частицы. Целью такого воздействия является снижение фрагментации сложных органических соединений при их ионизации и, в перспективе, регистрация и идентификация единичных бактерий.

Kochevalina, M. Y., Bukharina, A. B., Trunov, V. G., Pento, A. V., Morozova, O. V., Kogun, G. A., Simanovsky, Ya. O., Nikiforov, S. M., Rodionova, E. I. (2022). Changes in the urine volatile metabolome throughout growth of transplanted hepatocarcinoma. *Scientific Reports*, *12*(1), 1-10.

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МАСС-СПЕКТРОМЕТРИЯ БЕЛКОВ ЯДРА ДЛЯ ОПРЕДЕЛЕНИЯ МЕХАНИЗМОВ ИНДУЦИРОВАННОЙ ГРАНУЛОЦИТАРНОЙ ДИФФЕРЕНЦИРОВКИ ЛЕЙКОЗНЫХ КЛЕТОК

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Исследования индуцированной гранулоцитарной дифференцировки помогают выявить молекулярные механизмы созревания клеток. Ядерный протеом представляет собой источник регуляторных молекул, в том числе транскрипционных факторов (ТФ). Кроме того важно иметь представление о молекулярных пертурбациях на ранних стадиях дифференцировки клеток. Мы применили масс-спектрометрическое профилирование с использованием изобарных меток (TMT) для исследования ядерного протеома лейкозных клеток линии HL-60 под действием полностью-*транс*-ретиноевой кислоты (ATRA). В результате было определено 214, 319, 376 и 426 белков с измененным содержанием в 3, 6, 9 и 12 ч после обработки ATRA, соответственно, по сравнению с контролем. С точки зрения молекулярных функций, 231 белок из 1860 идентифицированных ядерных белков обладал активностью транскрипционных факторов (ТФ). При этом содержание шести ТФ (RREB1, SRCAP, CCDC124, TRIM24, BRD7 и BUD31) было снижено, а содержание трех ТФ (EWSR1, ENO1 и FUS), напротив, повышено в ранние временные точки (3–12 ч) после обработки ATRA. Биоинформатический анализ ядерного протеома показал обогащение белками, вовлеченными в репарацию ДНК, сигнальный путь RUNX1 и регуляцию сигнального пути p53. С применением мониторинга выбранных реакций с использованием стабильных изотопно-меченых пептидных стандартов (SRM/SIS) было показано устойчивое увеличение содержания белков PRAM1, ТФ CEPBP, ТФ RBPJ и ТФ HIC1 в ответ на обработку ATRA. В то же время для ТФ STAT1 и белков CASP3, PARP1 и PRKDC наблюдалось транзиторное увеличение содержания в ядре только в ранние временные точки (3–12 ч) после обработки ATRA. Полученные для ядерного протеома качественные и количественные данные могут быть полезными для разработки новых подходов к лечению лейкозов. Исследование выполнено при финансовой поддержке Российского научного фонда, грант № 21-74-20122. Масс-спектрометрический анализ и хранение данных проводили на оборудовании Центра «Протеом человека» (ИБМХ).

ОПРЕДЕЛЕНИЕ СПЕЦИФИЧЕСКИХ БЕЛКОВ В СОСТАВЕ АМИЛОИДНЫХ ДЕПОЗИТОВ. ОСОБЕННОСТИ РАБОТЫ С РАЗНЫМИ ВИДАМИ МАТЕРИАЛА

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Амилоидозы представляют собой группу заболеваний, вызванных нарушением сворачивания белковых молекул и отложением их в виде нерастворимых агрегатов — амилоидных депозитов в различных органах и тканях. Данный процесс приводит к нарушению метаболизма в пораженном органе или системы органов, а затем к полиорганной недостаточности. Диагноз «амилоидоз» ставится на основании гистологического исследования биоптата пораженного органа, поскольку амилоидные депозиты обладают специфическим свойством окрашиваться Конго красным, с характерным яблочно-зеленым свечением в последующем исследовании окрашенного препарата в поляризованном свете. На данный момент известно более тридцати специфических амилоидогенных белков, способных формировать амилоидные агрегаты и определяющие тот или иной тип амилоидоза. Таким образом, постановка диагноза и дальнейшее лечение напрямую зависят от точности определения белка, формирующего амилоиды. Основным методом определения амилоидогенного белка, сформировавшего амилоидные агрегаты, а, следовательно, и определяющего тип амилоидоза долгое время являлся иммуногистохимический анализ. Однако, как оказалось, данный метод отличается низкой чувствительностью и специфичностью. В последние годы золотым стандартом для типирования амилоидоза стал масс-спектрометрический анализ белкового состава амилоидных депозитов.

В данной работе нами были отработаны условия для выделения тотального белка из различных препаратов (замороженные ткани, ткани, извлеченные из парафиновых блоков и соскобов со стеклопреапаратов). Для каждого типа препаратов были составлены протоколы пробоподготовки. Данные протоколы были использованы для проведения масс-спектрометрического анализа различных органов, полученных от пациентов с гистологически подтвержденным диагнозом «амилоидоз». На ряду с установлением структурных белков для различных типов тканей (ткани сердца, почки, подкожно-жировой клетчатки) были получены результаты по белковым составам амилоидных депозитов. Также нами были получены протеомы для соответствующих тканей, в которых отсутствие амилоидных депозитов было подтверждено с помощью гистологического исследования. С помощью данного подхода нами было установлено пять типов амилоидозов в различных препаратах. На данный момент мы продолжаем отрабатывать методики по определению белкового состава амилоидных агрегатов для пациентов с диагнозом «амилоидоз» с целью улучшения качества идентификации типа амилоидоза.

УЛЬТРАБЫСТРАЯ ХРОМАТОМАСС-СПЕКТРОМЕТРИЯ ДЛЯ МЕДИЦИНЫ И БИОЛОГИИ

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Профилирование протеома методами хроматомасс-спектрометрии (ЖХ-МС) широко используется для мониторинга физиологического состояния клеток и организмов. В последнее время идет активное развитие методов производительного протеомного анализа, предполагающего пропускную способность прибора в несколько сотен образцов в сутки. Нами был предложен метод DirectMS1, использующий 5-минутный хроматомасс-спектрометрический анализ с регистрацией спектров пептидов без их фрагментации, и разработано программное обеспечение для идентификации и полуколичественного анализа белков с контролем доли ложноположительных идентификаций (FDR). Мы продемонстрировали, что 5-минутный анализ на масс-спектрометре высокого разрешения типа Orbitrap и разделением по ионной подвижности позволяют идентифицировать ~ 2000 белков в протеоме клеток HeLa при 1% FDR. Показано, что результаты количественного анализа, полученные в режиме DirectMS1 не уступают по эффективности методам зависимого и независимого сбора данных (DDA, DIA). На данный момент метод DirectMS1 протестирован на применимость для анализа растительных тканей, микробных и злокачественных клеток. Идёт апробация метода для исследования микробиомов и физиологических жидкостей, таких как плазма крови. Мы полагаем, что DirectMS1 представляет огромный интерес для биологических и медицинских исследований с точки зрения быстрого и эффективного определения молекулярных маркеров, характеризующих физиологическое состояние живой системы.

ТЕХНОЛОГИЧЕСКАЯ ПЛАТФОРМА НА БАЗЕ МАСС-СПЕКТРОМЕТРИИ ДЛЯ АНАЛИЗА БИОЛОГИЧЕСКИХ ОБРАЗЦОВ

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Цель. Анализ биологических тканей методом десорбционной ионизации электрораспылением с целью диагностики и прогнозирования заболеваний.

Актуальность. В последнее десятилетие масс-спектрометрическая визуализация (MSI) все чаще используется исследователями для изучения распределения метаболитов, лекарств, пептидов и белков на поверхности тканей. Возможность применения MSI для однозначного картирования сотен биомолекул в одном анализе привела к тому, что этот подход стал использоваться в исследованиях раковых тканей. В работе рассматриваются различные методы масс-спектрометрической визуализации на примере исследования раковой ткани яичников. В последнее время значительно расширились области применения десорбционной ионизации электрораспылением (DESI). Эксперименты по визуализации тканей методом DESI можно проводить в условиях окружающей среды. Кроме того, он практически не требует подготовки образцов и является минимально инвазивным, что делает его пригодным для прямого анализа тканей. DESI-MSI может предоставить объективную информацию о биохимическом распределении молекул уже после одного измерения. Таким образом, этот метод обеспечивает надежное распознавание тканей и идентификацию биомаркеров, которые в будущем могут быть использованы для диагностики и прогнозирования рака.

Материалы и методы. Подготовка проб для анализа DESI намного проще, чем в других методах MSI. Образцы свежезамороженной ткани (в данном случае серозной карциномы яичника) подвергали криосрезу толщиной 10 мкм, а затем помещали на предметные стекла. Слайды хранились при температуре -80 ° C до измерений DESI. Для анализа DESI предметные стекла помещали на двухмерный линейный подвижный предметный столик и использовали программное обеспечение High Definition Imaging (HDI) 1.4 (Waters Corporation) для определения области, подлежащей визуализации. Распылитель DESI направлялся на эту область для получения масс-спектров, собираемых в заранее определенных координатах x и y с разрешением 100 мкм на масс-спектрометре Waters QTOF. Эксперименты DESI-MSI проводились в режиме отрицательной ионизации с диапазоном масс m/z 50–1000. МС данные были обработаны и визуализированы с использованием программного обеспечения HDI 1.4.

Результаты. Было обнаружено, что МС спектры содержат, в основном, липиды и жирные кислоты. Большинство идентифицированных липидов относились к классу фосфатидилэтаноламинов (ФЭ). Анализ методом основных компонентов (PCA) показывает четкое разделение между окружающей опухолью стромой и опухолевой тканью. Общая точность перекрестной проверки в классификации между этими двумя типами тканей достигала 100%. Наши результаты демонстрируют точное распознавание тканей и идентификацию ткане-специфических молекулярных ионов (биомаркеров) для образца ткани рака яичников с использованием масс-спектрометрии DESI. Опухоль и ассоциированная с опухолью строма имеют различные липидомные профили, богатые фосфатидилэтаноламинами. Предложенный нами метод масс-спектрометрической визуализации раковой ткани обладает многими преимуществами по сравнению с классическими методами MSI: минимальная подготовка образца, неразрушающий амбиентный метод, который позволяет проводить дополнительный анализ того же среза ткани, например, с помощью гистологического анализа, золотого стандарта онкологической диагностики. Анализ ткани методом DESI-MSI может быть полезным для уточнения фундаментальных вопросов образования, функционирования и прогрессии опухоли яичника. С помощью данного метода можно быстро получить набор специфических биомаркеров злокачественной ткани и наблюдать различия между нормальной и опухолевой тканью, что делает этот метод важным дополнением к классическим клиническим исследованиям.

METHODOLOGY AND TECHNOLOGY OF THE EXPERIMENT

PATHOLOGICAL PRION PROTEIN NANOSTRUCTURES, ISOLATED FROM HUMAN BRAIN TISSUE WITH CREUTZFELDT-JAKOB DISEASE

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Prion disorders are considered as a special class of human and animal diseases, associated with excessive accumulation in the central nervous system of aggregates of β-pleated sheets, called PrP_{Sc}, PrP_{d} or $PrP_{27\text{-}30}$ that are resistant to proteases. Here, we described some nanostructures, formed by $PrP_{27\text{-}30}$, using atomic-force microscopy.

Materials and methods. An autopsy samples of human brain tissues (n = 2), who died with clinically diagnosis of Creutzfeldt-Jakob disease (CJD), were subjected for analysis.

Atomic force microscopy. Tapping mode cantilever NSC15/Al BS were used. Topographic images of various pathological prion nanostructures, deposited on a hydrophilic mica surface, were obtained using a Nanoscope IIId MultiMode microscope (Bruker, USA).

Results. Using atomic force microscopy (AFM) the nanostructural analysis was carried out, which made it possible to characterize the nanogeometry parameters of prion rods (R_a — 0,87±0,05 nm, R_q — 1,12±0,09 nm, the coefficient of skewness — 0,84, $R_{min\text{-}max}$ — 1,12-8,74 nm), as well as amyloid fibrils (R_a — 0,90±0,05 nm, R_q — 1,54 ± 0,09 nm, the coefficient of skewness — 0,48, $R_{min\text{-}max}$ — 2,46-6,72 nm). The presence of polymorphism in the surface relief of high molecular weight fibrillar prion structures with a predominance of smoother areas was shown. The «quasi-forms» of amyloid fibrils, differing in height and surface-relief microprofiles, were revealed, which indicates heterogeneity in the packing of protein domains in the composition of high molecular weight prion structures.

HENRY'S LAW AND DECOMPRESSION SICKNESS: WHY STUDYING MEDICAL BIOPHYSICS IS IMPORTANT

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In the first year of studying biophysics, many medical students ask themselves questions: what happens to human blood when the environmental pressure changes?

The answer is that a sudden decrease in ambient pressure causes decompression sickness in a person: a large number of gas bubbles form in the person's blood and as a result, blood flow is blocked. Decompression sickness can lead to paralysis or death.

The occurrence of decompression sickness explains Henry's law. When the ambient pressure rises, the gas inhaled by the person has a higher pressure than the pressure of the gas in the blood. A diffusion gradient of gas into liquid is created. Under normal conditions, the gas does not enter the blood, but with a sharp increase in pressure, the gas dissolved in the blood begins to rapidly release, forming bubbles. Blood cells attach to the vesicles and blood clots form, which clog the blood vessels and destroy their walls. As a result, bleeding occurs, the blood supply to vital organs is disrupted; gas embolism may occur.

By asking questions about the causes and manifestations of various diseases, medical students learn to solve the problems of diagnosing and treating diseases based on biophysical laws.

STUDY OF SUITABILITY FOR 3D BIOPRINTING OF THE SYNTHESIZED GELMA-BASED HYDROGEL WITH A HIGH DEGREE OF SUBSTITUTION

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A wide range of technologies are used to create scaffolds, in particular, 3D bioprinting. The advantage of GelMA compared with other bioinks is the ability to control mechanical properties by changing the concentration, degree of functionalization, types of photoinitiators and irradiation time.

The percentage of DoF for the synthesized and commercial gels was 82.75 ± 7.09 and 79.44 ± 3.56, respectively. The viscosity of 7.5-15% gelatin solutions begins to increase sharply at temperatures below 32°C. The viscosity of GelMA at 21°C remained low, indicating a serious change in rheological properties after gelatin functionalization. Thus, in order to maintain printability, it may be necessary to use combined solutions based on GelMA and unmodified gelatin, or to print at temperatures close to 0°C. Lines of a given height were printed in one layer at different speeds from 5 to 20 mm/s with a step of 2.5 mm/s. Printing was reproduced over the entire range of speeds. In order to evaluate printing at an angle, a model with several types of angles was developed. The layer height error will accumulate and distort the object. The area of the object after printing differed from the given value (0.640 cm^2) by 12.7%, and after incubation by 28.1%.

In this study, a series of experiments was carried out to study the characteristics of the synthesized GelMA hydrogel and its suitability for printing. We obtained highly substituted 82.75 ± 7.09 GelMA that can be used for 3D-bioprinting.

IL1RL1(ST2) — NEW MARKER OF ADVERSE CARDIOVASCULAR EVENTS AND CORONARY DISORDERS IN INDIVIDUALS WITH INCREASED STRESS ON THE CARDIOVASCULAR SYSTEM

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Abstract. According to modern authors, in a hypertrophied heart, intense blood circulation predominates, due to which the functional capabilities of a sports heart become less stable. To date, myocardial hypertrophy is one of the predictors of coronary heart disease and congestive heart failure, in addition, an increase in myocardial mass with characteristic non-adaptive remodeling is a predictor of sudden cardiac death.

A recent systematic review has shown that prolonged training without adequate recovery predisposes not only to myocardial hypertrophy but also to myocardial fibrosis. Myocardial fibrosis is a complex process of increasing the volume of collagen in the myocardium due to damage to the heart muscle that occurs during inflammation, heart remodeling in response to hypertonic overload or myocardial fibrosis.

According to a 2017 meta-analysis conducted by the Harvard Clinical Research Institute, encoded IL1RL1(ST2) gene is a predictive independent cardiac biomarker for remodeling and myocardial fibrosis in patients with heart failure.

Context/Purpose: In connection with the above, this study is aimed at early diagnosis of pathological conditions of the cardiovascular system, by determining the concentration of soluble IL1RL1(ST2) and a comprehensive examination of the cardiovascular system in athletes involved in martial arts.

Methods: This is a prospective non-randomized study with the participation of 30 male athletes. The study was conducted on the basis of the Centre for Sports Medicine and Rehabilitation (Almaty, Republic of Kazakhstan). To

determine the clinical and prognostic significance of the soluble form of IL1RL1(ST2) as a marker of heart failure, myocardial hypertrophy and fibrosis in the early diagnosis of pathological conditions of the cardiovascular system in athletes involved in martial arts.

Results: To determine the level of sST2 expression in blood serum, first the serum ST2 level in volunteer (VO) at rest and in athletes in before training was analysed. The results showed that sST2 levels were significantly higher (*p* d™ 0.001) in the before training 548.1 ± 32.6 pg / mL group than in the volunteers 337.1 ± 61.8 pg / mL. Serum sST2 level for after training 830.01 ± 71.6 pg / mL was significantly higher than before training (*p* d™ 0.001).

Interpretation: Athletes' sST2 levels exceeded thresholds both before and after training. Moreover, the relationship between an increase in ST2 levels and abnormal ECG abnormalities and a high level of stress in athletes was determined. ST2 concentration was associated with cardio-pulmonary stress triggered by the cumulative exercise dose as well as with lifelong psychological stress.

Conclusion: Our findings indicate that the elevated ST2 concentrations in athletes could be used as the predictive value. However, clinical relevance and results validity require further intensive studies.

MICROPARTICLES BASED ON CROSS-LINKED HYALURONIC ACID

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The trend of the last decade in pharmacology is the use of polymer nanoparticles and nanocapsules as means of targeted drug delivery to diseased organs, tissues, cells, and even specific intracellular compartments — organelles.

One of the most widely used biocompatible polymers for medical applications is hyaluronic acid (HA). It is a linear glycosaminoglycan built from repeating residues of D-glucuronic acid and N-acetyl-D-glucosamine. Hyaluronic acid is a biodegradable polyanion of biological origin, one of the main components of the human tissue extracellular matrix. It takes part in the regeneration of living tissue, maintaining the water and osmotic balance of the intercellular matrix. Hyaluronic acid is very widely used in plastic surgery to correct the shape of the soft tissues of the face by subcutaneous injections into the epidermis.

There are two main problems associated with corrective preparations (fillers) based on hyaluronic acid.

The first is the subcutaneous migration of fillers, which leads to a distortion of the shape of the face. This problem is solved by chemical cross-linking of the main chains of polyglycosaminoglycan, which reduces subcutaneous mobility and the rate of polymer biodegradation. Divinyl sulfone (DVS), 1,4-butanediol diglycidyl ether or water-soluble carbodiimides are commonly practiced.

The second problem is much more difficult. It is related to the fact that the quality and age of the skin varies greatly from patient to patient and the drug must be adapted in accordance with the condition and diseases of the skin of a particular patient. One of the approaches is the creation of fillers containing a "depot" of medicinal preparations, for which it is proposed to use drug-loaded nanoparticles and nanocapsules.

The aim of this work is the synthesis of nanoparticles and nanocapsules based on cross-linked hyaluronic acid loaded with anti-inflammatory drugs for the treatment of postoperative aseptic inflammation of the skin.

A NANOSCALE THERANOSTIC SYSTEM FOR CO-DELIVERY OF MAGNETIC NANOPARTICLES AND PACLITAXEL BASED ON HUMAN SERUM ALBUMIN

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Development of theranostics that integrate a combination of both therapeutic and diagnostic agents in a single nanoscale agent is among the most promising trends of nanomedicine [1]. The objective of this study was to develop human serum albumin-based nanoparticles for co-delivery of paclitaxel (PTX), a chemotherapeutic agent widely used for the treatment of breast cancer, and magnetic iron oxide nanoparticles (MNPs), a contrasting agent for MRI diagnostics. The human serum albumin nanoparticles (HSA NP) were obtained using the principle of nab™ technol-

ogy [2] that involved high pressure homogenization of the mixture containing HSA, paclitaxel, and MNP (obtained previously). The non-crosslinked HSA NP had a diameter of 100-130 nm, narrow polydispersity (PDI < 0.2), and a negative surface potential (-7.6 ± 0.9 mV) (Table 1). Decrease of the HSA:Fe mass ratio in the HSA NP from 400:1 to 200:1 led to decrease of their disintegration concentration from 25 μg/mL to 17.7 μg/mL (PTX conc.). The NPs containing 0.5% of Fe and ~10% of paclitaxel formed a suspension that maintained its stability for > 6 h. This is the first report describing the non-cross-linked HSA-based nanosuspension containing a MRI contrasting agent and PTX prepared using nab™ technology.

Table 1 — Physicochemical parameters of the HSA nanoparticles containing paclitaxel and MNP

HSA:Fe mass ratio (theor.)	HSA:PTX ratio (theor.)	HSA:PTX ratio	Z-aved, nm	PDI	PTX content, mg/mL	Disintegration conc. (0.9% NaCl), μg/mL
400:1	9:1	10.5:1	125 ± 1	0.160±0.002	3.89	25.0
200:1	9:1	11.6:1	102 ± 1	0.135±0.011	2.30	17.7

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MITOCHONDRIAL RESPIRATION OF PRIMARY NEURONAL CELL CULTURE UNDER THE INFLUENCE OF LEUTRAGINE

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The aim of the work was to study the mitochondrial respiration of the primary neuronal cell culture under the influence of the drug leutragin.

The primary neuronal cell culture was obtained from newborn one-day-old pups of transgenic mice of the Fus line (experimental group) and wild type (WT control group). The midbrain tissues were isolated by trypsinization followed by washing and resuspending in a growing medium. Cells were seeded in *Cell Culture Miniplate* (Seahorse, USA) at the rate of 40,000 cells per well. The cells cultivated for 7 days. After that, the drug leutragin at a final concentration of 100 nM, 1 mkM, and a control without the drug was added to the wells of culture plates. Cells were incubated with drug during 24 hours. A mitostress test was performed at the end of the incubation. The measurements were performed using the Seahorse Bioscience XF HS mini cellular metabolism analyzer (Seahorse Bioscience, Agilent, USA).

Under the influence of leutargin, proton leakage in the Fus and WT groups decreased by two times compared to the control. Maximal respiration was reduced in the WT group under the influence of the drug at a dose of 1 mkM, while in the Fus group no significant differences were found compared to the control. ATP production increased in the Fus group under the influence of the drug at a dose of 100 nM, in the WT group significant differences compared with the control were not.

Thus, considering that leutragine is an opioidergic regulator of cellular metabolism its depressing effect on mitochondrial function in wild animals (WT) and stimulation of ATP production in the transgene group (Fus) was established, probably due to the switching of metabolic pathways from aerobic respiration to anaerobic glycolysis.

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INTERACTION OF COBALT FERRITE MAGNETIC NANOPARTICLES IN HYDROPHILIC COATING WITH BILAYER LIPID MEMBRANES

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Magnetic nanoparticles are widely used in medical applications, for example, as contrast agents for magnetic resonance imaging, to enhance hyperthermia, for targeted drug delivery, theranostics (therapy + diagnostics). When used in vivo, magnetic nanoparticles require a special coating that promotes biocompatibility and minimizes potential toxicity under physiological conditions. Human serum albumin or polyethylene glycol can be used as a coating. In this work, the interactions of magnetic cobalt ferrite nanoparticles (12 and 27 nm size) with diphitanoylphosphatidylcholine bilayer lipid membranes were investigated. The conductivity of membranes varied over a wide range — two groups of membranes can be distinguished — membranes, the conductivity of which (after the addition of nanoparticles) remained practically unchanged compared to the control, and membranes, the conductivity of which, upon the addition of nanoparticles, changed abruptly and increased in a wide range by 0.5–2 orders of magnitude. Significant differences between the conductivities upon the addition of the same volume of 12 and 27 nm nanoparticles surrounded by human serum albumin were not found. When adding nanoparticles with a coating of polyethylene glycol, the conductivity increased much weaker than when adding nanoparticles with a coating of human serum albumin. The results suggest that hydrophilic coated magnetic nanoparticles interact with the membranes, which can lead to the appearance of metastable conducting pores, which, in turn, increase the integral conductivity of the membranes.

AGGREGATOMETRY IN THE EVALUATION OF PLATELET FUNCTION

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The risk of cardiovascular diseases has always been high, but the number of requests for medical help has increased against the background of complications after suffering Covid-19, especially the risk of thrombosis. The search for laboratory criteria for evaluating the effectiveness of antiplatelet drugs, which are often prescribed to patients at risk of thrombosis, is also relevant. An important problem is the study and understanding of the mechanisms of the ability of platelets to activate, their structural and functional changes, which will expand the possibilities for the prevention and correction of disorders in the hemostasis system. It is proposed to use various laboratory tests, however, at present, the generally accepted method in laboratory practice for assessing the aggregation function of platelets is aggregometry.

Depending on the material under study — whole blood or platelet-rich plasma, as well as the type of registration of measurements, impedance or optical aggregation is used, which has become widespread. The study of platelet aggregation with various types of inducers is of great importance both for characterizing the functional properties of platelets in case of suspected hereditary thrombocytopathy, and for the differential diagnosis of the pathology of the components involved in the implementation of platelet-vascular hemostasis. The complexity is both the choice of the inductor and the interpretation of the results. Clinical laboratories use the reference intervals specified in the reagent kit instructions or reference literature, however, this may lead to misinterpretation of the results. Foreign and domestic experts recommend that each laboratory establish reference intervals for each laboratory parameter or confirm those available in the reference literature. In this regard, at the moment it is relevant to develop standards for assessing platelet aggregation activity, which will help reduce the risk of thrombosis or bleeding in patients taking antiplatelet therapy.

ASSESSMENT OF THE RISK OF THE DEVELOPMENT OF CEREBRAL STROKE BASED ANALYSIS ON LIFETIME MODIFICATION DNA METHYLATION

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Background and Objectives. Ischemic conditions (IC) are characterized by relative or absolute insufficiency of blood supply, which is manifested not only by local tissue hypoxia, but also by other metabolic disorders due to insufficient intake of nutrients. The most common pathological conditions in ischemia are coronary heart disease (CHD) and cerebral stroke (CS). The study of in vivo modification of the DNA methylation profile in IS is a new area of scientific interest.

Purpose. The main goal of this study is to evaluate the lifetime profile of DNA methylation among patients with ischemic conditions and among healthy people based on bioinformatic analysis of GEO projects and molecular genetic analysis of CpG dinucleotides.

Methods. Bioinformatics analysis was performed for three GEO projects — GSE69138, GSE40279 and GSE55673 (total number of individuals> 2.5 thousand). Molecular genetic analysis to determine the level of DNA methylation (CpG dinucleotides) was performed using SNaPshot™ technology (Thermo Fisher Scientific, USA) for 36 patients with CS and for 32 individuals from the comparison group (without a history of chronic diseases). Statistical analysis was carried out using SPSS v.20.

Results. Statistical and bioinformatic analysis of GEO projects was performed, which resulted in the formation of a list of CpG dinucleotides, that methylation profile in total, had a high predictive ability in the context of assessing the risk of developing CS.

Based on the performed bioinformatic analysis, molecular genetic studies were carried out for patients with CS (venous blood samples were provided by the Republican Scientific and Practical Center «Kardiology», Minsk, Belarus) and methylation levels for 5 CpG dinucleotides were calculated: cg03488097 — 47.99±8.60%, cg19743406 — 71.67±6.60%, cg25845688 — 62.62±15.50%, cg03071146 — 72.55±10.69% and cg08224066 — 87.10±8.95%. Similar values for the comparison group: cg03488097 — 47.23±8.19%, cg19743406 — 67.11±7.72%, cg25845688 — 51.60±16.42%, cg03071146 — 71.59±8.31% and cg08224066 — 81.15±8.41%. Statistically significant differences were found for cg03488097 (F=9.632, p=0.004, pLevene=0.304), cg19743406 (F=6.91, p=0.011, pLevene=0.214), cg25845688 (F=8.103, p=0.006, pLevene=0.496), cg08224066 (F=7.915, p=0.006, pLevene=0.399).

Conclusion. Based on bioinformatics, molecular genetics and statistical analysis, CpG dinucleotides were identified, the methylation profile of which is statistically significantly associated with CS. Further research will be aimed at expanding samples and developing a model for assessing the risk of developing CS.

Conflict of interests. The authors declare no conflict of interests.

POLYMER COMPLEXES OF 5-FLUOROURACIL BASED ON POLYANIONS WITH THEIR OWN IMMUNOSTIMULATING ACTIVITY

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Introduction. One of the promising and relevant directions in the treatment of oncological diseases, at present, is the use of polymer complexes of antitumor agents. Polymer derivatives contribute to changes in pharmacokinetics, reducing the effect of the drug on healthy cells, which leads to a decrease in toxicity.

The aim of the work is to obtain and study complexes of 5-fluorouracil (5-FU) with methacrylic acid polymers.

Materials and methods. To obtain polymer complexes, a polymer carrier was used, represented by polymethacrylic acid, a 5-FU substance. As a result of the physicochemical interaction of the carboxyl groups of the polymer with 5-FU, polymer complexes were formed. Evidence of the formation of polymer complexes with 5-FU is the data of IR and UV spectroscopy. The degree of 5-FU release was determined in a buffer solution at pH = 5.4 and 7.4 in a dialyzer.

Results. The obtained data on the release kinetics show that the release of the polymer complex with 5-FU in an acidic medium (at pH = 5.4-5.5) is higher than in a slightly alkaline (at pH = 7.4) medium. Thus, in an acidic environment inside the tumor cells, the drug substance will be released, and in the bloodstream the drug substance is in a bound state with a polymer carrier, which prevents the risk of toxicity.

NANOPARTICLES FOR INTRA-NUCLEAR DRUG DELIVERY

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Effective gene therapy is possible only with the use of carriers capable of delivering drugs or genes into the cell and its organelles at different stages of development. The purpose of the work was to study the possibility of drug delivery into the nucleus of living cells at the stage of mitosis.

Doxorubicin is an antitumor antibiotic. It was used as a model compound due to the fact that the penetration of this substance into the cell can be easily detected by confocal fluorescence microscopy during in vitro studies. Synthesized polycyanoacrylate particles obtained from adduct of ethyl-2-cyanoacrylate and fatty acids were used as a carrier. Ethyl-2-cyanoacrylate monomers have a number of unique properties, the main one is the ability to polymerize, in the absence of radical initiators, with the formation of polymers capable of biodegradation inside the body (by hydrolysis and enzymatic hydrolysis). The surface of the particles was covered with a layer of polysaccharide (dextrane) and phosphatidylcholine in order to ensure the affinity of the surface with the cell membrane for better penetration.

The best result was obtained with nanosised polymeric carriers of small diameter (100 nm) and with a surface charge close to neutral. The particle size was determined by dynamic light scattering. Such systems are able to penetrate inside the cell and also deliver substances into the nucleus at the stage of mitosis; at other stages of cell development, they are inert and not able to interfere with the processes of cellular metabolism.

However, the antitumor drug doxorubicin is only a model compound. In the future, such polymeric carriers are planned to be used for a wide variety of physiologically active substances.

WETLAB AS A PRIORITY AREA IN PEDIATRIC SURGERY

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The purpose of the study: to present options for surgical techniques on experimental animals in the modeling of congenital and acquired pathology.

Materials and methods: The WetLab course is conducted on the basis of the educational laboratory of the Volga Research Medical University. Wistar rats (weight 150-250g) and Soviet Chinchilla rabbits (weight 3.5 — 4.0 kg) are used as laboratory animals. Anesthesia is carried out with drugs Zolazepam (25 mg / kg) and Xylazine hydrochloride (3 mg / kg). Operations are performed by open and minimally invasive methods (laparoscopic stand “Endomedium”). To conduct training operations, a permit was issued by the local ethics committee of the Federal State Budgetary Educational Institution “PIMU” of the Ministry of Health of the Russian Federation (Protocol No. 5 of 10.03.2021).

Results: The list of surgical interventions in rats includes: laparotomy, under optical glass (2.5x / 3.5x) anastomosis, formation of intestinal stomas, modeling of ischemia with subsequent measurement of blood flow and collection of morphological samples.

The anatomy of a rabbit has a similar structure to a human, therefore, on this model it is possible to work out the stages of abdominal operations, such as: access to the main neurovascular bundles, stopping bleeding in a wound, ligation of vessels under a clamp, laparotomy, revision of the abdominal cavity, tracheostomy, conicotomy, appendectomy, nephrectomy, splenectomy, cholecystectomy, gastrostomy, excretion intestinal stomas (sigmostoma, ileostoma, eunostoma), the imposition of gastro-entero- and interstitial anastomoses, hemostatic sutures on the liver, suturing of perforations, wounds, sanitation and drainage of the abdominal cavity.

Within the experimental laparoscopic operating room, a wide range of minimally invasive interventions is also possible: laparoscopic access, revision of the abdominal cavity, appendectomy, nephrectomy, splenectomy, cholecystectomy, suturing of the perforation of the hollow organ, extraction of the drug through the trocar, sanitation and drainage of the abdominal cavity.

Conclusions: Thus, WetLab is a modern and promising direction in the framework of teaching surgical skills.

BIOPHYSICS AND MEDICAL STATISTICS AS THE BASIS OF EVIDENCE-BASED MEDICINE

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It is important for future doctors to study medical biophysics in combination with other academic disciplines, in particular with medical statistics. This allows you to draw reasonable conclusions that form the basis of evidence-based medicine.

For example, the analysis of integral hemodynamic parameters of patients is based on the use of statistical approaches. Quantitative calculations make it possible to reveal the difference in central hemodynamics in the group of healthy individuals and in the group of patients with arterial hypertension.

In both groups, a decrease in minute volume of blood causes an increase in peripheral resistance and stiffness of the arterial system. According to the studied indicators, hyperkinetic, eukinetic, hypokinetic types of central hemodynamics of patients can be distinguished.

In healthy individuals and patients with hypertension with different hemodynamic types, there are significant differences in the integral indicators of central hemodynamics.

Ensuring the constancy of blood pressure indicators with a decrease in the “minute volume of blood” indicator is possible with an increase in the periphery of vascular resistance and stiffness of the arterial system.

MONITORING ACTIVITY-DEPENDENT PLASTICITY OF POSTSYNAPTIC DENSITY IN UNIDIRECTIONAL NEURONAL NETWORK IN VITRO

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Postsynaptic density (PSD) consists of a set of proteins that are involved in formation and stabilization of ion channels, receptors and other structures required for synaptic transmission. Changes of PSD morphology are often associated with activity-dependent synaptic plasticity. Recent development of microfluidics methods has made it possible to construct modular neural networks in vitro with synaptic connectivity similar to in vivo. Such modular structure of the neural networks are promising models for studying the basic mechanisms of brain network functioning. This work is aimed to develop and test a method to estimate activity-dependent changes in PSD of neurons that form intermodular connections in vitro.

Mice hippocampal cells (E18) were cultured on 60-electrode arrays (Multichannel systems, Germany) combined with microfluidic chips, which provide unidirectional axon growth. Transduction of hippocampal cultures with FU(PSD-95:EGFP)W (provided by prof. Noam E. Ziv, Israel) lentiviral system (Invitrogen, USA) was performed on 4 –5 day in vitro (DIV). Images were acquired with x40 magnitude (Celldiscoverer 7, Germany). To silence network activity, we used a mixture of 1 μM TTX, 50 μM CNQX, 50 μM CPP on 17 DIV. We estimated the sizes of the PSD on the dendrites in the chip microchannels before and after blocking the activity.

The morphological changes of PSDs were observed on a time scale of several days. The proposed method is convenient for future studies of activity dependent plasticity in modular neural networks of various cell types in health and disease.

The study was supported by the Russian Science Foundation, project 21-75-10154.

ACQUISITION OF CHONDROSPEHERES FOR CARTILAGE BIOPRINTING

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In order to get chondrospheres, perspective for bioprinting 2 methods have been used. Chondrocytes were taken from human cartilage tissue. 1st method included using silicone molds in agarose forms. Hot 2% agarose solution was poured into the mold MicroTissues 3D Petri dish after cooling down agarose forms were placed in 12 well plate

and filled the well with DMEM medium and incubated it for 30 mins, then medium was removed and forms were filled with cell suspension using different concentration 1000, 3375, 8000, 16000 и 27000 cells per spheroid, after that forms were incubated in 37°C and 5% CO_2. 2nd method included low adhesive plates according to manufacturer instruction. Cells were added into the wells of plate with same concentrations 1000, 3375, 8000, 16000 и 27000 cells per spheroid.Plates were incubated in 37°C and 5% CO_2. Acquired spheroids were studied morphometrically to check diameter, round shape, also we studied kinetics of flattening in adhesive wells, kinetics of fusion, biomechanical properties.

Both methods allow to get large quantities of chondrospheres. Chondrocytes from agorose forms had bigger spread of sizes and were problematic to watch with the microscope, probably the reason was manual form making with some roughness on the surface. So method with low adhesive plate was considered as better one.Cell concentration 8000 cells per spheroid was the most optimal one as it covers biggest square and does not cause necrosis in the middle of the sphere.

THE EFFECT OF THE POLISACHARIDE LAYER ON THE PARTICLES FORMATION AND SIZE

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Nowadays target drug delivery system is the method for delivering physiologically active substances to the target site of action or site of absorption. It allows increase the concentration of delivered substances in the targeted parts of the body and reduce side effects of the drug on healthy organs and tissues. Nanoparticles are one of the most promising types of drug delivery systems. The advantages of these nanocarriers are their ability to control drug release rate. In the work the polymer nanoparticle consists of two layers. The inner layer is formed by adduct of ethyl-2-cyanoacrylate and octyl alcohol and the outer polysaccharide layer was variable. All selected polymers are biocompatible, non-toxic and biodegradable. The main characteristics of such systems that affect their effectiveness are particle size and surface charge. Depending on the selected polysaccharide the formation of particles and their size were studied.

HYBRID NANOPARTICLES MODIFIED WITH A FLUORESCENT BISPHOSPHONATE DYE: A VERSATILE TOOL FOR BONE-TARGETING

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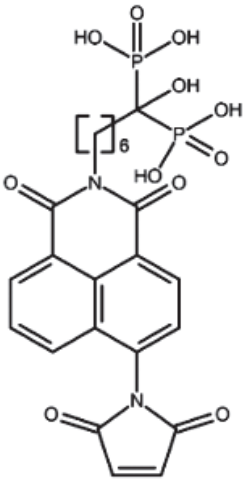
Bisphosphonates (BP) are widely used in the treatment of bone disorders due to their high affinity to Ca^{2+} ions [1]. Development of drug delivery systems based on polymeric nanoparticles (NPs) modified with BPs is a promising approach to bone-targeting therapy [2]. Furthermore, employment of the fluorescently labeled BP-modified NP would enable visualization of the bone resorption site. In this work, the hybrid PLGA-HSA NP were labeled using a novel fluorescent naphthalimide dye with a bisphosphonate group (Dye1, Fig. 1).

First, the PLGA-HSA nanoparticles with a poly(lactic-co-glycolic acid) core (PLGA, Purasorb PDLG 5004A) and a shell consisting of human serum albumin (HSA) were prepared using a high pressure homogenization technique. The albumin shell provides functional groups on the surface and simultaneously reduces opsonization in the blood plasma. For fluorescent labeling of the PLGA core, the PLGA carboxylic end group was conjugated with a Cy5 fluorescent dye prior to to the particle formation [3]. HSA was immobilized on the PLGA surface during the NPs formation (0.1 mg HSA/mg PLGA). First, the amine groups of HSA were thiolated using a Traut's reagent and then the Dye1 with maleimide groups was added for thiol-maleimide conjugation.

The PLGA-HSA-Dye1 NPs had a diameter of 143 nm, narrow polydisperisty (PDI 0.058), and a negative zeta-potential of -37.3 mV. The NPs contained 1 μg Dye1 per 1 mg of and exhibited good fluorescent properties.

Figure 1: Dye1 (λex 346 nm, λem 396, 467 nm)



The core-shell PLGA-HSA nanoparticles conjugated with a fluorescent biphosphonate derivative exhibit suitable parameters for nanoparticle-based delivery and represent a promising tool for bone-targeting therapy and diagnostics.

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The study was funded by Ministry of Science and Higher Education of Russian Federation as part of FSSM-2020-0004 state project.

CREATION AND MATURATION OF SPHEROID-CONTAINING TUBULAR TISSUE ENGINEERING PERIOSTEUM CONSTRUCTS IN THE AEROSOL OF A CULTURE MEDIUM

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Tubular forms of spheroid-containing tissue engineering constructs require the development of special production methods. We suggest that a controlled mechanical flexion of the scaffold plate with adhered spheroids in the aerosol of a culture medium will enable us to effectively produce a tubular construct with an intact outer layer and obtain a biomimetic connective tissue cover (periosteum) with regenerative potential.

The periosteum cell culture was derived from the cambium layer of the periosteum in rabbit tibia. Cell spheroids were created in agarose wells (MicroTissues Inc.®). The scaffold plate was a membrane of Type 1 collagen in the form of fibers obtained by electrospinning (Прогресс4Био® / Progress4Bio®). A frame was installed onto the scaffold; inside the frame, spheroids were placed in a thick row. After tissue fusion of the spheroids and their partial penetration into the scaffold (5 days) we began to roll up the construct using a special device inside an author-developed tissue engineering bioreactor with aerosol delivery of the culture medium. On day 5, 10 and 15 the construct was evaluated by morphological, immunohistochemical and biochemical methods.

During controlled flexion of the construct each individual spheroid stretched, flattened and polarized, maintaining viability throughout the observation period. As a result, the spheroid layer formed a kind of sleeve around the scaffold — maintaining the volume, integrity and architectonics of the tissue fusion between all spheroids in the layer.

Therefore, a combined tissue engineering construct of periosteum spheroids and scaffold can be rolled up by the application of controlled mechanical forces that influence the size and shape of the spheroids. Using the culture medium aerosol makes the construct easier to manipulate and enables us to maintain the viability of spheroid cells and their involvement in morphogenesis until the edges of the scaffold are fully joined together.

This study was carried out as part of government-assigned research and development at the FGBU Central Research Institute of Traumatology and Orthopaedics of N. N. Priorov of the Russian Ministry of Health.

INFRARED THERMOGRAPHY OF THE HAND

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Medical infrared thermography is a registration method of the natural thermal emitting of the human body in the invisible infrared region of the electromagnetic spectrum. The temperature dynamics of the surface of the human body at rest under thermoneutral conditions are determined mainly by peripheral blood flow controlled by the degree of the vasoconstriction, which is controlled almost entirely by the sympathetic nervous system in response. The purpose of our research was to measure and compare surface temperature of the hand front and back. Infrared thermometer brand UNI-T (China) was used in our study for body temperature measuring. The experimental group consists of 13 volunteers (8 women and 5 men) 20 to 23 years. The hand front and back surfaces temperature was measured with three different thermometers 5 times for each person. We used Excel for statistical data processing. The average temperature was 31,62 и 31,18 °C for hand front and back surfaces accordingly. The one is higher because of the presence of superficial and deep palmar arterial arches in it. The obtained result is of the scientific interest and requires further analysis and comparison with the results of other studies.

The authors express their gratitude to the head of the Department of Medical and Biological Physics.

SURFACE AND STRUCTURE OF PHOSPHATIDYLCHOLINE MEMBRANES RECONSTRUCTED WITH $COFE_2O_4$ NANOPARTICLES

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Structural changes in phosphatidylcholine lipid membranes caused by introduction of insoluble $CoFe_2O_4$ nanoparticles (NPs) are analyzed. Changes in nuclear magnetic resonance spectrum, infrared spectrum and ionic conductivity of membranes are observed with NPs added. The presence of NPs in membranes is proved by atomic force and magnetic force microscopy. Structural changes in the membranes in the vicinity of the lipid C-O bonds caused by NPs are observed by Scanning Near-Field Optical Microscopy. Analysis of NMR spectra allowed us to identify the affected atomic groups in the membrane surface layers. Conductivity measurements of the bilayer membranes were performed in DC as well as in time resolved modes. Hydrophobic NPs stimulate surface distortion and creation of pores, which depending on NPs concentration leads to an increase of membrane ionic conductivity. Concentration dependence demonstrating percolation threshold was analyzed in the frame of fractal theory approach. Following main results were obtained.

Addition of the $CoFe_2O_4$ magnetic nanoparticles to the lipid phosphatidylcholine bilayer membrane does not change the properties of NPs. Separate NPs are visualized in the membrane by AFM and MFM techniques as well as by TEM technique. Suspending in the lipid does not affect saturation magnetization of the ferromagnetic NPs, which demonstrates that NPs are not solvated (Fig.1).

Coercive field of NPs increases in membrane solution due to fixation of the particles preventing their rotation in magnetic field. This fixation appears due to bond formation between lipid molecules and NPs.

1. Structure of lipid membranes changes under NPs deposition. Lipid layers, where the tails of the lipid molecules are located demonstrate changes in the FTIR spectra at wavenumbers 980 cm^{-1} and 1025 cm^{-1} corresponding to Fe — OH and Fe–C-H bonds formation. Visualization of membrane areas at these wavenumbers by s-SNOM microscopy reveals distorted structure of the membrane around individual NPs.
2. Redistribution of integral intensities of the lines in NMR spectra indicates structural changes of membrane area, where lipid tails are located. Atoms of the $^0CH_3$–CH_2–groups are involved in the formation of Fe — OH and Fe = C-H bonds between lipid and NPs as detected by FTIR. The newly appearing lines correspond to alkyl H–C–H or –NH groups disturbed by NPs in the bulk part of the membrane. Formation of hydrogen bonds between NPs

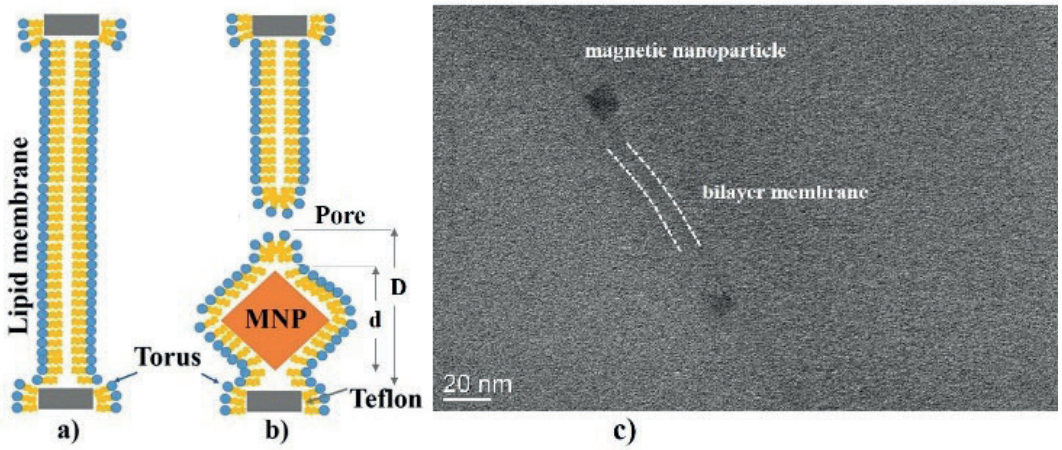

Fig.1. Phosphatidylcholine bilayer membrane formed over a diaphragm hole between sections of the teflon chamber (a); lipid membrane with magnetic nanoparticles of diagonal *d* and a pore creating the area of enhanced conductivity of diameter *D* (b); TEM image of NPs in bilayer membrane (c).

and lipid is confirmed by NOESY NMR technique manifested by de-shielding of the closely located ^{1}H nuclei in the membrane structure perturbed by NPs.

Structural rearrangement of the membrane in the presence of $CoFe_2O_4$ NPs leads to ca. 10-fold increase of ionic conductivity of phosphatidylcholine bilayer lipid membrane at an average distance between the nanoparticles of 0.25 μThe concentration dependence of conductivity corresponds to percolation transition realized by infinite fractal of fractional dimensionality $2 < \varepsilon < 3$. The electrical percolation threshold happens when ~ 0.2% coverage of the membrane surface is reached. Infinite fractal appears at ~ 50% coverage of the membrane by large ~ 100 — 200 nm crossing AEC surrounding small NP's of 14 nm diagonal.

DEVELOPMENT OF BIODEGRADABLE TUBULAR SCAFFOLD FOR SMALL DIAMETER VASCULAR GRAFTS

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The disadvantages of coronary artery bypass grafting with autologous peripheral veins are mainly associated with the difference in the biomechanical properties of arteries and veins, which determines the relevance and practical significance of the development of synthetic grafts of small diameter (less than 5 mm).

Materials and methods. Tubular scaffolds with inner diameter of 2 mm were made by electrospinning using a 10% solution of polycaprolactone (PCL) in CH_2Cl_2 at the NANON-01A installation (Japan). Mechanical tests were carried out on the Shimadzu Uztest EZ-SX bursting machine (Japan). The bioactive layer was created from heparin and human platelet lysate. Cytotoxicity and hemolytic activity of the scaffolds were evaluated using NIH/3T3 mouse fibroblasts and rabbit blood, respectively.

Results. Scaffolds obtained from 2 ml of PCL solution at feed rate of 4 ml/h had the physicomechanical properties closest to native blood vessels: Strain at rupture — 235 ± 75%; Tensile strength — 5.2 ± 0.9 N; Young's modulus — 1.9 ± 0.1 MPa. To reduce the detected high water permeability of the scaffolds (from 42.3 ± 3.7 ml/(cm^2 min) to 3.4 ± 0.1 ml/(cm^2 min)), a three-layer scaffolds was made with the addition of a water-resistant layer from a mixture of PCL with gelatin (30% gelatin by polymer weight), which did not affect the physical and mechanical characteristics of the samples and their biocompatibility.

Conclusions. Three-layer biocompatible tubular scaffolds from PCL with a water-resistant middle layer from PCL and gelatin with physicomechanical properties close to coronary vessels and low water permeability have been developed.

THE OBTAINMENT OF DECELLULARIZED PANCREATIC SCAFFOLDS FROM PANCREAS WITH STRUCTURAL CHANGES

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A significant deficit of donor organs limits the possibility of obtaining a sufficient amount of tissue-specific scaffold for creating a tissue-engineered pancreatic construct. Therefore, it is important to investigate the possibility for decellularization of donor pancreas unsuitable for transplantation due to structural changes.

Objective: to develop an optimal protocol for decellularization of human pancreas with different morphological characteristics of the native tissue.

Methods. A tissue-specific scaffold was obtained as a result of physicochemical methods of decellularization under various modes of pancreatic tissue treatment, including cyclic repetition of freezing and thawing, treatment in solutions with increasing concentration of surfactants or treatment in a 0.1% solution of sodium dodecyl sulfate in low and high ionic strength in different sequences.

Results. Three types of pancreatic tissue samples were identified: pancreas with evident lipomatosis signs, pancreas with diffuse fibrosis, and pancreas without pronounced signs of structural changes. Histological analysis showed that the protocol with using freeze and thawing cycling is suitable only for the human pancreas with lipomatosis; the protocol with using osmotic shock is suitable for the pancreas with diffuse fibrosis and pancreas without pronounced signs of fibrosis and lipomatosis, but with a different sequence of processing steps.

Conclusions. The conducted studies have shown that in order to carry out complete decellularization of human pancreatic tissue, the protocol of the treatment method must be correlated with the features of the structure and composition of the native tissue. The possibility of using morphologically altered pancreas, unsuitable for transplantation, to obtain tissue-specific scaffold is shown.

IMAGING HALLMARKS OF SARCOMA PROGRESSION VIA X-RAY COMPUTED TOMOGRAPHY

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Abstract. Sarcomas represent the largest group of rare solid tumors that arise from mesenchymal stem cells and are a leading cause of cancer death in individuals younger than 20 years of age. Errors in the diagnosis of sarcomas, which reach up to 30%, limit the number of therapeutic modalities and catastrophically worsen the prognosis. The development of an algorithm for the early accurate diagnosis of sarcomas seems to be as important as the development of novel therapeutic advances. We summarized the findings of recent studies on imaging sarcoma progression using X-ray computed tomography in preclinical studies and current clinical practice. In preclinical studies, PET/CT in vivo imaging provides an assessment of sarcoma progression and metastasizing processes. Furthermore, we hypothesize that micro-CT enables the visualization of neovascularization and stroma formation in sarcomas, including the novel techniques of whole-block and whole-tissue imaging, which seem to be a necessary tool for histopathological specimen examination due to the variety of histological sarcomas' subtypes. We supposed that multimodality imaging should help to invent new effective therapeutic modalities which will be precisely targeted for various aspects of sarcoma progression. Also, finding correlations between CT, PET/CT, and micro-CT imaging features may significantly increase the accuracy of soft-tissue and bone tumor diagnostics, which leads to the initiation of appropriate histotype-specific management in a timely manner and, consequently, to improved outcomes.

THE FUNCTIONAL ACTIVITY EVALUATION OF THE AUTISTIC CHILDREN COMPLEMENT SYSTEM BY ANALYZING ITS EFFECT ON *TETRAHYMENA PYRIFORMIS*

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The kids Autism Spectrum Disorders (ASD) is an amount of mental disorders which is characterized by atypical behavior and social communication problems. Such pathologies are able to be accompanied by epilepsy, depression, anxiety, hyperactivity and attention deficit. As a rule, children with ASD reveal the immune system dysregulation, children with this disorder are likely to be overly susceptible to viral and bacterial infections, which indicates the body's defense mechanisms violations also the complement system.

The complement system (CS) takes the lead in regulating the immune system participants interactions. The assessment of the entire system functional activity is more representative than its individual components concentrations measurement. The faCS parameter was used for this assessment which is calculated by the formula:

faCS=100*(1/T50), where T50 is the death time of a half of the model unicellular organism cells initial number in a solution with 1.25% serum/plasma concentration.

Previously, we have confirmed that the death of Tetrahymena pyriformis protozoa in serum or plasma solutions is associated with the CS action. An automated method for faCS assessing is a cyclic counting of live ciliate cells in serum or plasma solutions. The method is supplied by the Biolat device by means of the AutoCiliata program.

Comparative research of faCS in plasma and serum were held on 64 children with ASD and 28 mentally normal children of the same age. Comparisons between groups were performed by the Statistica10 program using the nonparametric Mann-Whitney method.

In accordance with the Mann-Whitney U-criteria it was established the difference between the group of children with ASD and the group of neurotypical children $Z=4.43$, $p<0.001$, which means the intergroup differences are statistically significant. As to 67% of children with ASD the functional activity of CS in the blood serum is below normal. In the neurotypical group only 17% of the total number differ from the norm.

The estimation of the plasma component of hemostasis (coagulation) contribution to the CS functional activity level was assessed by comparing faCS in serum and plasma for each blood sample. For neurotropic patients the difference between faCS in plasma and serum is little (up to 20%) while complement activity is higher in plasma than in serum in all of them. For children with ASD serum and plasma faCS levels differ significantly — for 52 children with ASD the plasma faCS level is 40-90% higher than in serum, for 7 children with ASD the serum faCS level is higher than in plasma and for 3 children with ASD these levels are the same. The different involvement of coagulation in a CS activation is to indicate the features of immune disfunction.

So, the functional activity of the complement system assessment and serum and plasma compare of this parameter is able to be the marker of the ASD children immune system features.

METHOD OF MANDIBULAR SECTIONS TOPOGRAPHY FOR DENSITOMETRY ON POSITRON EMISSION TOMOGRAPHY SCANS

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The invention (RU №2779366) belongs to medicine, in particular to radionuclide diagnostics, dentistry, radiology and can be used for individual topography of mandibular areas suitable for densitometry on positron emission tomography (PET-CT scans).

The method of topography of areas of the mandible for densitometry on PET-CT scans is as follows.

1. The patient is examined with a standard PET-CT scan on a 64-slice tomograph 60-90 minutes after fluorodeoxyglucose radiopharmaceutical is injected.
2. Using the navigation system, the mandible is located on the axial section of the obtained 3D-image.
3. On the axial section, by scrolling the computer mouse roller on the mandible, find the upper edge of the mental foramen and the plane of transition of the mental foramen to the mandibular canal.
4. Find the required plane under the mandibular canal by scrolling the roller of the computer mouse for 3-4 mm.

5. Rounded bone areas in the projection of central incisor roots and premolar roots of 0.6-1.2 cm^2 area are selected in this sought plane with the help of a virtual ROI (region of interest) tool.

Optimal areas of mandible for densitometry are found. The proposed method allows a radiologist, oncologist, oncologist-chemotherapist to quickly find the optimal area on the mandible for densitometry, including during treatment with osteomodifying agents. This method can be used to diagnose drug-induced osteonecrosis at an early stage.

ASSESSMENT OF THE LEVEL OF CHLORIDES IN THE BLOOD DURING EXPERIMENTAL MODELING OF PHYSICAL DEPENDENCE ON ALCOHOL

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The relevance of the study is associated with the high prevalence of alcoholism worldwide. According to the literature and in the practical aspect of alcoholism therapy, special attention is paid to electrolyte metabolic disorders. Experimental modeling of alcohol dependence with subsequent determination of electrolyte metabolism indicators allows us to exclude the influence of additional factors inherent in human alcohol consumption and objectively assess the contribution of changes to the pathogenesis of alcoholism. The purpose of the study: to find out the serum level of chlorides in the conditions of an experiment on animal alcoholization.

Materials and methods: the model of experimental alcoholism according to Abdrashitov A.H. et al. was used. (1987). Animals intragastrically received the 25% ethanol solution in half a half-year dose per day for five days, followed by withdrawal from the experiment on the first day of the formation of the ethanol withdrawal reaction (8g / kg / day, group A, n = 7). In the group of intact animals, distilled water was administered in an equivalent volume (group K, n=8). Determination of the chloride level was carried out photometrically at a wavelength of 492nm. In the statistical processing of the data obtained, the following were applied: a) indicators of descriptive statistics: median, upper and lower quantiles; b) non-parametric Mann-Whitney criterion (U) to assess the significance of differences for independent samples.

Results and discussion: The concentration of chlorides in blood serum in group A animals was 139.7 (146.3; 139.1) mmol/L and was statistically significantly (pU=0.008) higher than group K data by 67.3%. Alcohol-associated pathology, in addition to obligate involvement in the pathological process of the nervous and cardiovascular systems, includes kidney damage by the type of glomerulonephritis with a violation of the corresponding functions of the nephron. In this regard, it can be assumed that the detected changes in serum chloride levels during the ethanol withdrawal reaction are associated with impaired renal function.

Conclusion: The results obtained indicate an increase in the level of chlorides in the blood serum in the alcoholization experiment, which may be associated with the formation of changes in the excretion of chlorides in the renal tubules, leading to an increase in their concentration in the blood.

IR DYNAMIC THERMOGRAPHY AS A DIAGNOSTIC METHOD

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Infrared thermography is an innovative approach in medicine based on registration of the object's own radiation in the infrared range, which indicates the safety of the method in relation to humans. It is widely used for diagnostics of neurological, vascular, oncological and other diseases. Numerous studies in infrared thermography are currently underway. It should be noted that this method has limitations that do not allow it to be used as an individual diagnosis, but only in conjunction with other types of research.

A cell, tissue, organ or system of organs has its own blood supply system, which is disturbed during the development of a pathological process of this or that etiology, which certainly affects the energy supply of the organ. This indicates the change of temperature indices both in the place of pathology occurrence and outside its limits, thus indicating the spread of this process through the organism. Due to redistribution of blood supply, change of its intensity, increase or decrease of temperature is registered, which is a target for the thermograph.

In our study, an experiment was conducted to measure the intensity of blood circulation in the hand area by performing a stress test. Seventeen subjects participated in the experiment: 11 women and 6 men between the ages of 19 and 22 years, none of them being professional athletes. Each performed the same instructions. Subjects had their pulse measured at rest and palm temperature measured at rest, then a stress test was performed: hand clenching and unclenching for one minute. After the exercise, the temperature and pulse were measured again. According to the results obtained, no significant changes in temperature and pulse were registered during this exercise.

Thus, the results of the experiment showed that there is no relationship between the change in temperature and the change in pulse after exercise.

EXPRESSION OF SENESCENCE-ASSOCIATED β-GALACTOSIDASE IN REGENERATING ELASTIC CARTILAGE. MORPHOLOGICAL STUDY

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Lysosomal enzyme senescence-associated(SA) β-galactosidase is expressed in senescence cells. The mechanisms of cellular senescence are activated after mechanical damage in regenerating tissues. Thus they influence the rate of cartilage regeneration depending on the term and the diameter of the mechanically inflicted defect.

The aim is to study the expression level of SA-β-galactosidase depending on the term of regenerating elastic cartilage and the diameter of the mechanically inflicted defect.

Cryosections of exit wounds samples of rabbit ears of various diameters and terms were made: 4mm (group 1), 6 mm (group 2), and 8 mm (group 3) on the 30th, 60th, and 90th day. Then they were stained to identify SA-β-galactosidase and analized by morphometrics.

As a result, the highest level of SA-β-galactosidase expression in senescence cells was in group 3 on the 30th day. The cartilage regenerated at a faster rate. The level of SA-β-galactosidase expression decreased in all the groups on the 60th day, and this can be explained by their elimination by immune cells. The lowest activity of SA-β-galactosidase and the largest regenerated area were in group 2 on the 90th day. In group 3, the level of SA-β-galactosidase expression was five times higher than in group 2.

After damage, senescence cells accelerate cartilage regeneration and inhibit it with prolonged persistence.

DOUBLE-LAYER POLY (2-CIANOACRYLATES) NANOCAPSULES AS A CARRIER FOR INTRACELLULAR DELIVERY OF POLYNUCLEOTIDES

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Currently, one of the important directions in pharmacology is the intracellular delivery of DNA. Particles enter the cell by three mechanisms. Micelles with a diameter of 20-50 nm penetrate into the cell, avoiding the mechanisms of phago- and pinocytosis, but it is possible to exchange the contents of particles between themselves and ambient medium. Nanocapsules with size 200 nm and larger penetrate the cell by the mechanisms of phago- and pinocytosis with the formation of phagosomes and subsequent attack by lysosomal enzymes and splitting of the capsule. Multilayer carriers with a size of about 100 nm are able to penetrate into the cell due to the fusion of the surface membrane with the plasmoleme, while the content of the carrier enters the cell. In this case, phago- and pinocytosis do not occur.

Successful intranuclear DNA delivery requires nanoparticles about 100 nm in size with an outer layer similar in structure to a cell membrane, and they must also have an internal solid layer that excludes the possibility of exchanging the content of nanoparticles between themselves and the ambient medium.

DNA can be encapsulated in double-layer poly-2-cyanoacrylate nanoparticles. The material of the solid wall is ethyl-2-cyanoacrylate, and the outer shell, similar in structure to the cell membrane, consists of phosphatidylcholine structured with cholesterol. The size of the obtained nanoparticles was ranged from 100 to 400 nm (DLS). The average degree of encapsulation was 95%. A fish DNA preparation «Derinat» was used as a model drug.

IN VITRO MODEL OF DAMAGE AND RECOVERY OF A SEQUENTIAL NEURAL CIRCUIT

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Understanding mechanisms involved in the damage and recovery of axons in trauma is important for development of medical therapeutic solutions. We present a new concept of an *in vitro* experimental model of axonal injury in sequential neural circuits and recovery by new neuronal cells.

Mouse neocortex cells (E18) were cultured in a specially designed polydimethylsiloxane microfluidic chip consisting of three compartments for cell bodies sequentially connected by microchannels for axon growth. The axons of neurons from the first chamber grew through microchannels into the middle chamber and then into the third chamber, forming a predominantly unidirectional connection of two subnetworks. The middle chamber was used for axotomy at a distance of 400 μm from the cell bodies, simulating the conditions of axonal injury.

We tested two methods of axon injury: based on osmotic pressure and vacuum aspiration. For the first case, deionized water was poured into the middle chamber with axons for 5 minutes. For the second case, the culture medium in the middle chamber was completely removed for 2 minutes. Due to the high hydraulic resistance, parts of the axons inside the microchannels remained intact. The second method does not disturb the permeability of microchannels for growing axons.

To restore a unidirectional neural circuit, new neuronal cells can be loaded into the middle chamber. This model is designed to study the recovery of neuronal connections in the nervous system using transplantation of neurons obtained from induced pluripotent cells.

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АНАЛИЗ ПОВЕРХНОСТНО-УСИЛЕННОГО РАМАНОВСКОГО РАССЕЯНИЯ ПЛАЗМЫ КРОВИ ПАЦИЕНТОВ С ПОЛИПОМ, ГИПЕРПЛАЗИЕЙ В СРАВНЕНИИ С КОНТРОЛЬНОЙ ГРУППОЙ

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В настоящее время рак эндометрия является наиболее распространенным раком половых органов в развитых странах. Некоторые типы гиперплазии эндометрия могут прогрессировать до этого злокачественного новообразования. Диагностика рака эндометрия и гиперплазии (предраковых состояний) основана на гистопатологической оценке образцов тканей затратной по времени, которая является субъективной и вызывает расхождения в повторной оценке. Следовательно, существует необходимость в создании методов объективной оценки, позволяющих диагностировать ранние изменения. Исследование посвящено анализу Рамановскому рассеянию плазмы крови с последующим многомерным анализом (PLS-DA) спектральных данных для диагностики рака эндометрия, гиперплазии и нормальной контрольной группы.

Регистрацию и анализ результатов поверхностно-усиленного рамановского рассеяния осуществляли с использованием коллоидных серебряных наночастиц и микроскопической системы. Анализ спектральных характеристик анализируемой коллоидной среды проводили на экспериментальном стенде, состоящем из спектрометрической системы (EnSpectr R785, Spektr-M, Черноголовка, Россия) на основе ПЗС-детектора и микроскопа (ADF U300, ADF, Китай). Спектры возбуждались в ближнем ИК диапазоне с помощью лазерного модуля с центральной длиной волны 785 нм.

В результате с помощью метода PLS-DA, точность разделения Рамановских спектров полипа относительно контрольной группы и гиперплазии для калибровочного и проверочного набора достигает 83% и 81%, соответственно. Также были рассчитаны значения точности выделения контрольной группы относительно гиперплазии и полипа — 64-71% и гиперплазии относительно полипа и контроля 64-67%. Стоит отметить, что это предварительные исследования, которые показывают возможность обнаружения заболеваний и потенциал метода для диагностики конкретных типов заболеваний.

РАЗРАБОТКА МЕТОДА ПРОГНОЗИРОВАНИЯ ЭФФЕКТИВНОСТИ ПЛАЗМОННОЙ ФОТОТЕРМИЧЕСКОЙ ТЕРАПИИ ОПУХОЛЕЙ У ЛАБОРАТОРНЫХ ЖИВОТНЫХ

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Цель исследования — разработка метода прогнозирования эффективности плазмонной фототермической терапии (ПФТ) у крыс с перевитой холангиокарциномой.

Материалы и методы. Допплерографическое исследование опухолей проводили у 12 крыс с перевитой холангиокарциномой на ультразвуковой системе Voluson E8 Expert (GE Healthcare, США) с использованием режима энергетического допплера на частоте 7,2 МГц. Для оценки степени васкуляризации опухоли использовали программное обеспечение VOCAL (Medison-Kretz) с определением объема и индекса васкуляризации опухоли. После допплерографии крысам проводили трехкратные ежедневные внутривенные инъекции покрытых полиэтиленгликолем золотых наностержней в дозе 0,4 мг/мл и через 24 ч облучали опухоли чрескожно диодным инфракрасным лазером 808 нм в течение 15 мин при плотности мощности 2,3 Вт/см^2. Мониторинг нагрева опухоли осуществлялся с помощью тепловизора IRI4010. Эвтаназию животных и забор образцов опухолевой ткани проводили через 24 ч после ПФТ. Накопление золота в опухолях оценивали методом атомно-адсорбционной спектроскопии. Проводили стандартное морфологическое исследование тканей опухоли и иммуногистохимическое исследование с антителом к CD31 с оценкой микрососудистой плотности в опухоли.

Результаты. По данным энергетической допплерографии, индекс васкуляризации был равен нулю в небольших опухолях, при увеличении размера опухоли индекс васкуляризации повышался, при объеме опухоли 10 см^3 и более, индекс васкуляризации перевитых опухолей снижался за счет некротических изменений в опухоли. После ПФТ в опухолевой ткани наблюдались выраженные некротические изменения (до 90% площади). Было установлено, что накопление золота в опухоли и эффективность проведения ПФТ коррелируют с индексом васкуляризации и микрососудистой плотностью опухоли.

Выводы. До начала плазмонной фототермической терапии у крыс с перевитой холангиокарциномой рекомендуется проводить оценку васкуляризации опухолей с использованием режима энергетического допплера, повышение индекса васкуляризации свыше 0,155 свидетельствует о прогнозируемой эффективности ПФТ.

ИЗМЕРЕНИЕ ПОТЕРИ СЛУХА. МОДЕЛЬНЫЙ ЭКСПЕРИМЕНТ

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Введение. Потеря слуха является серьезной глобальной болезнью, которая затрагивает 360 миллионов человек во всем мире (ВОЗ, 2013). Потеря слуха — это неврологическая инвалидность, которая влияет как на физическое, так и на психическое благополучие пациентов. На базовом уровне потеря слуха является источником изоляции и депрессии для пациентов из-за важности слуха в общении. Людям с нарушениями слуха часто приходится в большей степени полагаться на тех, кто ухаживает за ними. Пациенты с потерей слуха подвергаются повышенному риску случайной травмы из-за потери этого чувства. Дети с потерей слуха подвергаются опасности снижения неврологического когнитивного развития в результате их ограниченного воздействия звуковых стимулов и языка. Потеря слуха представляет собой серьезное бремя как для пациентов, так и для медицинской системы. Поэтому ознакомление студентов 1 курса медицинских вузов с методами аудиометрии в рамках предмета физики является актуальной проблемой, решаемой данной работой. Ситуация часто осложняется отсутствием на кафедрах медицинской и биологической физики отсутствием специализированной аппаратуры.

В связи с этим определена **цель лабораторной работы**: смоделировать потерю слуха и узнать, при какой интенсивности она происходит у автора работы**.**

Материалы и методы: Для производства сигналов определенной частоты использовался генератор сигналов низкочастотный ГЗ-118 (производитель — Астэна, Россия) (рисунок 1).

Рисунок 1. Генератор сигналов низкочастотный ГЗ-118.

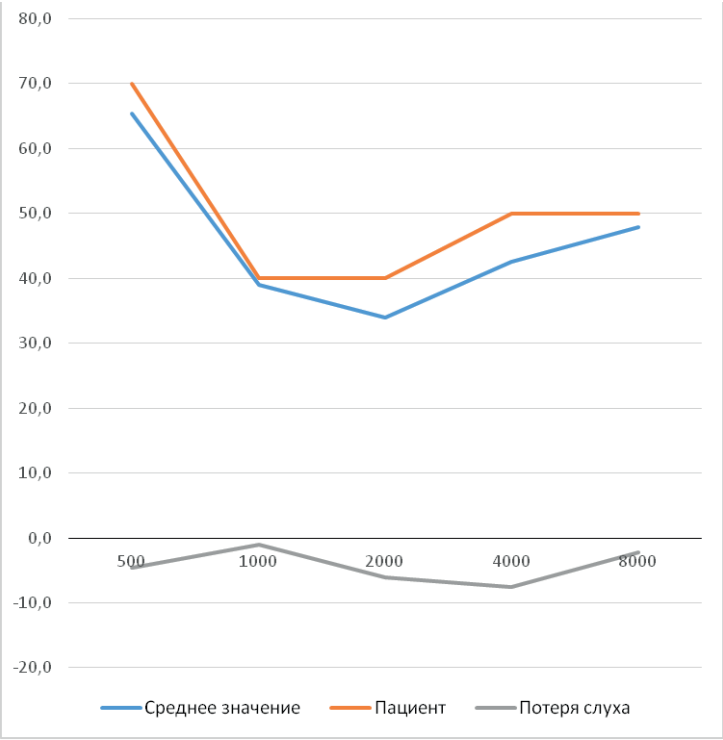
Для проведения эксперимента были отобраны 28 участников возрастом 17-18 лет (средний возраст 17 лет). Среди них 9 парней и 19 девушек.

Сначала участники эксперимента расположились на одинаковом, относительно близком, расстоянии от источника звука — генератора сигналов. Им предложили прослушать звуковые сигналы на разных частотах (500, 1000, 2000, 4000 и 8000 Гц) и с изменением интенсивности. После чего все записали полученные результаты, проанализировав которые мы смогли вычислить среднее значение нормы слуха. Интенсивность восприятия определялась путем вычитания уменьшения интенсивности от 70 дБ. Затем, чтобы создать модель потери слуха, участники эксперимента отошли от низкочастотного генератора на одинаковое, чуть большее, чем было изначально, расстояние, после чего проделали все те же манипуляции, что и в прошлый раз. В данном случае, значения были для каждого человека индивидуальными. И, наконец, чтобы найти значения потери слуха на разных частотах, мы из среднего значения нормы вычли значение, полученное при симулировании потери слуховой чувствительности. Все данные заносились в таблицу Excel (ссылка на Гугл диск: https://docs.google.com/spreadsheets/d/1Rdo5aD18Cx02JuxijYokeblYZ_dwwl3t/edit?usp=sharing&ouid=100339613776939758177&rtpof=true&sd=true).

Результаты. Данные о средней интенсивности звука в норме и значения для одного из пациентов при моделировании потери слуха.

Таблица 1. Интенсивность звука в норме и при потере слуха.

Частота	Нормы	Пациент	Потеря слуха
500	65,4	70	-4,6
1000	38,9	40	-1,1
2000	33,9	40	-6,1
4000	42,5	50	-7,5
8000	47,9	50	-2,1



По таблице был построен следующий график (рисунок 2).

Рисунок 2. График зависимости интенсивности звука в норме и при его потере от частоты.

Заключение. В ходе эксперимента была успешно смоделирована потеря слуха и определена интенсивность звука для каждой из определенных частот у автора работы в условиях потери слуха. Моделирование измерения потери слуха произведено адекватно, преимущество такого подхода в отсутствии сертифицированной аппаратуры для обучения.

Работа сделана на кафедре медицинской и биологической физики Сеченовского университета. Благодарим студентов групп 01-31 и 01-32 за участие в эксперименте.

МЕТОДИКА КОЛИЧЕСТВЕННОГО ОПРЕДЕЛЕНИЯ МАЛОНОВОГО ДИАЛЬДЕГИДА ВЭЖХ-МС/МС

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Малоновый диальдегид (МДА) является продуктом перекисного окисления липидов. Выступая в качестве сигнальной молекулы и маркера патологии, МДА имеет важное биологическое и клиническое значение. Стандартный метод определения МДА по реакции с тиобарбитуровой кислотой имеет невысокую специфичность и требует большого объема пробы, что затрудняет клинический анализ. Таким образом, не вызывает сомнения, что необходим поиск и разработка метода количественного определения МДА.

Цель работы — разработать и валидировать методику количественного определения МДА методом ВЭЖХ-МС/МС. Оценка концентрации МДА в транспортной среде (раствор Хэнкса («Sigma-Aldrich», Германия) с 25 мМ Хепес («Sigma-Aldrich», Германия) и 1% диметилсульфоксида («ПанЭко», Россия), тестируемая концентрация МДА) выполнялась методом ВЭЖХ-МС/МС с использованием хроматографической системы «Dionex Ultimate 3000» и тандемного масс-селективного детектора TSQ Fortis («ThermoFisher», США).

Хроматографию проводили на колонке UCT Selectra C18 4.6 mm×100 mm, 3um, 100A в комплексе с предколонкой Selectra C18 Guard Cartridges SLC-18GDC46-3UM; температура колонки 35 °C. Был использован изократический режим элюирования со скоростью потока 300 мкл/мин подвижной фазой, состоящей из 20% ацетонитрила и 80% водного раствора формиата аммония с концентрацией 10 мМоль/л.

Разработана и валидирована биоаналитическая методика количественного определения МДА методом ВЭЖХ-МС/МС. Предложенный метод определения МДА включает стадию высвобождения связанного МДА и исключает реакцию дериватизации. Нижний предел количественного обнаружения составил 600 нмоль/л, объем необходимой пробы 5 мкл, время анализа 7 мин. Полученный в ходе исследования диапазон концентраций дает возможность использовать данную биоаналитическую методику для определения концентрации МДА в биологическом материале при оценке физиологических и патологических состояний.

УЛЬТРАСТРУКТУРНОЕ ОБОСНОВАНИЕ МЕХАНИЗМОВ ВАРИКОЗНОГО РАСШИРЕНИЯ ВЕН РАЗЛИЧНОЙ ЛОКАЛИЗАЦИИ

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Введение. Современные трактовки патогенеза варикозного расширения вен (ВРВ) у пациентов молодого возраста позволяют установить генетически детерминированный характер процесса. ВРВ различной локализации относится к проявлениям синдрома НДСТ (по Т.И. Кадуриной).

Цель: доказать роль синдрома НДСТ в развитии ВРВ (при ВБВНК и ВЦ), посредством изучения биоптатов их стенок на ультраструктурном уровне.

Материалы и методы. Исследованы фрагменты стенок ВРВ от 15 пациентов мужского пола в возрасте 6-26 лет; выделены три группы пациентов: с ВЦ, с ВБВНК и группа контроля. Проведено электронно-микроскопическое исследование (ЭМИ) двух фрагментов мышечного слоя стенок вен: из наиболее широкого и истончённого участков.

Результаты и их обсуждение. При ЭМИ биоптатов стенок варикозно расширенных вен обнаружены схожие морфологические и морфометрические признаки как в разных возрастных группах, так и при разной степени выраженности заболевания, существенно отличающиеся от группы контроля. При оценке состояния пучков коллагеновых волокон (качественный параметр) наблюдался феномен «структурного хаоса»: неупорядоченное расположение, вариабельность их количества в пучках, неравномерная толщина, участки дезорганизации, расширение межволоконных пространств. Количественный морфометрический анализ выявил выраженную вариативность числового ряда при замере толщины пучков коллагеновых волокон, что указывает на первичную несостоятельность соединительнотканного каркаса стенок ВРВ. Результаты продольных и поперечных замеров ГМК в истончённых участках показали уменьшение объёма клеток по сравнению с контрольной группой; имело место избыточное разрастание коллагеновых между ними — вплоть до фор-

мирования соединительнотканных муфт, нарушающих контактность ГМК между собой. Расстояния между отдельными ГМК были значительно шире, чем в группе контроля.

Заключение: проведённый ультраструктурный анализ позволяет подтвердить роль синдрома НДСТ в патогенезе варикозной трансформации при ВЦ и ВБВНК; что даёт возможность объединения этих заболеваний в «болезнь варикозно расширенных вен».

КЛАСТЕРНЫЕ ТЕХНОЛОГИИ В ОЦЕНКЕ РЕМОДЕЛИРОВАНИЯ МАГИСТРАЛЬНЫХ СОСУДОВ ПРИ МУЛЬТИФОКАЛЬНОМ АТЕРОСКЛЕРОЗЕ

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Актуальность: При использовании сетевых технологий для улучшения внутригоспитальных информационно-дистанционных возможностей в оценке ремоделирования крупных сосудистых бассейнов при мультифокальном атеросклерозе наиболее востребовано внедрение кластерных ресурсов искусственного интеллекта с новыми клинико-диагностическими методами артериальной визуализации магистральных сосудов головного мозга и нижних конечностей [1-3].

Цель исследования: Одноцентровое изучение особенностей ремоделирования магистральных бассейнов брахиоцефальных и переферических артерий нижних конечностей у больных мультифокальным атеросклерозом (МФА).

Материалы и методы: В зависимости от преимущественного поражения сосудистого бассейна больные методом иерархического анализа категориальных переменных были разделены на 3 кластера согласно клинической манифестации атеросклеротического поражения сердца (1-й кластер — 96 человек), головного мозга (2-й кластер — 96 человек) и артерий нижних конечностей (3-й кластер — 96 человек), подтвержденных коронароангиографией, ультразвуковой доплероскопией магистральный артерий головы и нижних конечностей.

Результаты. По данным УЗДС сонных артерий (СА) средняя степень стеноза общей сонной артерии (ОСА) преобладала у больных 1 и 3 кластеров — (23,28±17,52% и 35,34±12,31% справа) и (18,89±14,33%; 24,65±15,57% слева), что свидетельствовало о тенденции к большей выраженности поражения ОСА у них в сравнении со 2–ым кластером (p_{3-2}=0,0000), которое более значимо отмечалось справа. Стенозирующее поражение СА среди больных 2–го кластера выявляли реже, и значимость стенозов была ниже. Однако у 25% исследуемых выявили увеличение толщины комплекса интима-медиа (ТКИМ) сонных артерий 1,3 мм и более, что расценивали как признак атеросклеротического поражения ОСА. Данные УЗДС общих бедренных артерий (ОБА) у больных МФА высокого риска показали, что у пациентов 1-го кластера средняя ТКИМ правой ОБА составила 1,118±0,181 мм, 2-го кластера — 1,077±0,217 мм, 3-го кластера — 1,159±0,141 мм. Увеличение ТКИМ обусловлено развитием атеросклеротического поражения ОБА, которое преобладало у больных 3-го кластера по сравнению со 2-ым кластером ($P_{4-3=}$0,0283). При сравнении объемной скорости кровотока получены результаты, свидетельствующие о более низком ее уровне у больных 3-го кластера (0,522±0,146 м/с) по сравнению с 1-ым кластером (0,626±0,105 м/с), $P_{2-3=}$0,0002. Гемодинамически значимым изменением левой ОБА было также значительное преобладание больных 3-го кластера с увеличением ТКИМ (1,221±0,077 мм), что было сопоставимо со снижением у них объемной скорости кровотока (0,537±0,147 м/с) по сравнению с 1-м и 2-м кластерами — 0,642±0,079 м/с и 0,634±0,085 м/с ($P_{2-3=}$0,0001, $P_{3-1=}$0,0001).

Выводы: при внедрении сетевых технологий взаимодействия для улучшения внутригоспитальных информационно-дистанционных возможностей в оценке ремоделирования магистральных сосудистых бассейнов при мультифокальном атеросклерозе целесообразно использование кластерных ресурсов искусственного интеллекта с проведением ранней диагностики с помощью современных методов ультразвуковой визуализации сосудов, учитывая уровни стенозов, объемные скорости кровотока и гемодинамически значимые особенности поражения крупных артерий головного мозга и нижних конечностей, которые являются традиционными маркерами высокого риска сердечно-сосудистых событий.

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PERSONAL MEDICAL ASSISTANTS

INDIVIDUALIZED SURGICAL TREATMENT STRATEGY FOR EARLY-STAGE LUNG CANCER: TRANSLATION OF KNOWLEDGE

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As the popularity of lung cancer screening using low-dose computed tomography, an increasing number of early-stage lung cancers, featured by ground-glass opacities (GGOs), are detected. Unlike traditional treatments for lung cancer, GGO-featured lung adenocarcinoma defines a unique clinical subtype, which does not require bronchoscopy, brain MRI, or PET-CT as preoperative work-up. Sublobar resection with selective or no mediastinal lymph node dissection is recommended for GGO-featured lung adenocarcinoma, and a less intense follow-up plan is suggested. Since lung adenocarcinoma follows a stepwise progressive trajectory in pathology and radiology, early intervention of progression should provide excellent survival. Adenocarcinoma in situ and minimally invasive adenocarcinoma in pathology, as well as pure GGO and heterogenous GGO have a postoperative 5-year recurrence-free survival (RFS) of 100%, achieving definite cure. We defined the above periods with 100% RFS as curative surgical time window. To avoid overdiagnosis and over treatment while utilizing curative surgical time window, the relationship between estimated life expectancy and natural course, node location, node progression rate should be carefully evaluated before surgery. Persistent and slowly progressed GGOs required surgical resection, and artificial intelligence and liquid biopsy could be used as methods to predict progression. The above treatment strategy of early-stage lung adenocarcinoma will help us to refine our knowledge to the next level.

TENSOMETRIC SENSORS FOR DETERMINING PATHOLOGICAL CHANGES IN CARTILAGE

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Restriction of joint mobility is a universal symptom characteristic of many pathologies and diseases in cartilage. If not treated at this stage, the disease will progress. When carrying out diagnostic and therapeutic measures, it is important to provide accurate feedback to assess the success of treatment.

Stretchable and wearable strain gauges have been intensively studied in recent years for use in human movement monitoring. They overcome the rigidity limitations of traditional sensors, can be attached to the human body due to elasticity and biocompatibility, and provide high measurement accuracy through flexible contact.

In this work, a system consisting of strain gauge sensors is developed to record pathological changes in cartilage. The sensors consist of electrically conductive networks of carbon nanotubes, which provide high sensitivity, and polydimethylsiloxane elastomer, which provides high flexibility and biocompatibility of sensors. By attaching the sensors to the articular cartilage, joint mobility can be monitored over time, which provides important information for diagnosing and monitoring the effectiveness of the treatment of pathologies. The principle of operation of the sensors is to change the electrical resistance of the sensor material when it is deformed. The software block of the sensor displays the curve of the amplitude of articular cartilage movements in real time on the computer screen.

The developed sensor system is a portable compact device that can be used both in the doctor's office and independently to monitor the dynamics of articular cartilage pathology.

PRELIMINARY STUDY RESULTS USING PERSONALIZED REMOTE MONITORING IN PATIENTS WITH SKIN TOXICITY

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Background: The limited availability of medical care during a pandemic provokes the medical community to develop online programs for remote monitoring of patients. The effectiveness of online programs has been proven by a number of studies in the field of oncodermatology.

Purpose: The purpose of the study is to create and test the "Healthy Skin" service program, designed to monitor patients receiving anticancer therapy that cause skin toxicity.

Methods: Patients aged 18-70 with skin lesions associated with the use of anticancer therapy were divided into two groups. Group 1: 70 patients receiving remote monitoring using the developed program with a frequency of 1 time per week. Group 2 (control): 70 patients receiving face-to-face consultations with a dermatologist in accordance with the guideline of the oncological community. The sample was calculated on the basis of the general population. The severity of skin lesions in both groups of patients was assessed according to the NCI-CTCAE v5.0, World Health Organization's Quality of Life (WHOQOL-26), The Dermatology Life Quality Index (DLQI).

Results: In group 1, the frequency of failures and interruption of therapy is 12 times less than in the comparison group. The development of skin toxicity > 2 severity was 12.3% in the control group, compared with 1.2% in the group receiving remote monitoring.

Conclusions: Thanks to the personalized remote monitoring, the approach to diagnosing skin toxicity, continuous monitoring and timely maintenance therapy will be maximally optimized, it will avoid unreasonable interruptions and/or cancellations of anticancer therapy and improve the quality of life.

THE SIGNIFICANCE OF SUBCHONDRAL REMODELING IN THE ONSET OF PRIMARY GONARTHROSIS

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Relevance. The pathogenesis of early gonarthrosis stages remains debatable, and the significance of subchondral remodeling in inflammatory destruction of articular cartilage is controversial.

Material and methods. We examined 61 patients with 0-I radiographic stages of primary gonarthrosis and 10 healthy individuals aged 41.5±10.2 years using clinical and laboratory methods. BMD was measured with d*ual-energy absorptiometry. Serum* concentrations of osteocalcin N-Mid Osteocalcin Elisa (IDS), type I collagen fragments Serum CrossLaps (Nordic Bioscience Diagnostics, Denmark), and bone alkaline phosphatase MicroVue Bone Health (BAP, USA) were used to assess bone metabolism. Cartilage destruction was determined by the level of Urine Carti laps CTX II urinary excretion (ELISA, Nordic Bioscience Diagnostics, Denmark).

Results. We observed an increase ($p<0.05$) of Serum CrossLaps 0.811 (0.629; 0.971) ng/ml, BAP 32.79 (26.66; 38.09) u/l, excretion of Urine Carti Laps 28.4 c.u./day in the patients of both genders as compared to those in the controls: 0.401 (0.278; 0.392) ng/ml, 24.2 (21.78; 25.63) u/l, and 12.9(14.8; 19.2) ng/ml, respectively along with the unchanged BMD. The significant ($r=0.65$) positive ($p<0.05$) correlation between Serum CrossLaps and CTX II was detected.

Conclusion. The early stages of primary gonarthrosis feature dissociation of bone formation and bone resorption. We revealed the interplay of the signs of subchondral remodeling and articular cartilage destruction at the onset of the disease.

POSSIBILITIES OF VIDEOCAPILLAROSCOPY IN DERMATOLOGY

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Background: Specific vascular patterns in skin tumors are important for determining malignancy in noninvasive differential diagnosis of benign and malignant tissues. Accurate mapping and quantitative analysis of vascular morphology can significantly improve the effectiveness of diagnosis compared to traditional methods.

Purpose: Development of a new method for diagnosing diseases at an early stage.

Methods: We applied our visualization setup and processing algorithm to compare the image packages of skin lesions in the area of pigmented and pigmented-free benign formations, and then to calculate vascular maps based on comparative patterns of traditional dermatoscopy.

Results: Obtained vessel maps have high contrast of microvascular patterns evenly throughout the image both in and outside the pigmented area of skin lesions. Microvascular map in nevus with no abnormalities consists of punctate and tortuous vessels. Symmetry and uniformity of punctate vessels location is an important criterion for differential diagnosis of Spitz and dysplastic types. High spatial resolution provided by experimental setup enables vessels visualization even in small nevi, which is especially important for the early diagnosis of skin diseases.

Conclusions: The proposed technique can complement the traditional types of diagnostics of skin formations and become especially effective in the early stages of diseases. Analysis of the calculated vessel maps allows judging skin properties, pigment distribution and depth of vessels in the inspected area, for example, a microvascular rarefaction may indicate a significant thickness of the skin corneous layer.

DEVELOPMENT OF INTELLIGENT PERSONALIZED CONTACTLESS DIAGNOSTIC SYSTEMS WITH 24/7 OPERATION

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The demographic forecast of Rosstat until 2036 shows that in the coming years there will be a decrease in the population in Russia. The creation and introduction into practice of personalized intelligent diagnostic health management systems will lead to the solution of this problem. The system should include the following blocks.

1. Intelligent systems for analyzing output data.
   - 1.1. Contactless diagnostic sensors (heart rate, respiratory rate, frequency of blinking and pupil movement, temperature, skin color, puffiness, geo-positioning, voice analysis, gait analysis ...).
   - 1.2. System for collecting and analyzing psychoemotional and social data (psychotype, moral and volitional qualities, stress, intelligence, attention, memory, education, wealth, position, friends, family, children...).
2. External data analysis systems.
   - 2.1. Lifestyle analysis system (physical activity, quality and quantity of food (calories), quality and quantity of sleep, analysis of the daily routine, identification of stress factors, bad habits, indicators of intellectual activity).
     - 2.1.1. System for searching and analyzing patient data from open sources (social networks, contacts, geolocation, search engine queries) in order to determine the lifestyle, preferences, hobbies, desires, etc....
   - 2.2. Environmental factors analysis system.
   - 2.3. Passive system for analyzing genetic predispositions (if there is information about genome sequencing).
   - 2.4. System for analyzing the quality of medical care.
   - 2.5. System for analyzing psycho-emotional and social status.
3. The system of processing input and output parameters.
   - 3.1. The system of selecting the optimal perception channel for the supply of control actions.
   - 3.2. The system of issuing recommendations and building an individual health-saving trajectory (control action).
   - 3.3. The system for evaluating the implementation of recommendations.
   - 3.4. The system of development and presentation of motivational incentives (the possibility of creating a team score for the best implementation of recommendations, team play).

IMMUNE PARAMETERS IN ASSESSING THE DYNAMICS OF CLINICAL SEVERITY OF PATIENTS IN THE ACUTE PERIOD OF ISCHEMIC STROKE

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Introduction. The involvement of immune mechanisms in the pathogenesis of ischemic stroke (IS) determines the need to study immune parameters as predictors of the course and outcome of the disease.

Purpose: to study the relationship between inflammatory and autoimmune blood markers and the dynamics of neurological deficit in patients with IS.

Materials and methods: 22 patients with IS (60±5.5 years) were examined on the 1st and 10th days of the acute period of the disease (according to the ESS and the NIHSS scales). In blood of patients on the 1st day of observation, the activity of leukocyte elastase (LE) and α1-proteinase inhibitor (α1-PI), as well as antibodies (Abs) to S100B and MBP were determined. The control group consisted of 35 healthy people.

Results. Depending on the dynamics of neurological symptoms by the 10th day, two groups of patients were identified. Group 1 (n=10) was characterized by the normalization of the neurological deficit and an increase in LE activity and the level of Abs to MBP in blood of patients compared with controls and Group 2. In Group 2, the negative dynamics of the neurological deficit (n=12) was associated with a high α1-PI activity and insufficiently increased LE activity compared with controls. Using regression analysis, a mathematical model was developed to predict the development of the early post-stroke period (cut-off value: 0.5; sensitivity: 77.8%; specificity: 83.3%): $p = 1/(1+e^{-Z})$ 100%; $Z = -10.9+0.03 \cdot LE-0.17 \cdot \alpha1\text{-}PI+9.1 \cdot S100B+7.4 \cdot MBP$.

Conclusion. The studied immune markers can be considered as predictors of the course and outcome of IS.

РАЗРАБОТКА МОБИЛЬНОГО ПРИЛОЖЕНИЯ ДЛЯ СКРИНИНГА ОСЛОЖНЕНИЙ САХАРНОГО ДИАБЕТА

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Актуальность. На текущий момент в нашей стране зарегистрировано почти 5 миллионов больных сахарным диабетом (СД). Множество данных пациентов подвержено риску несвоевременного выявления осложнений СД.

Цель. Разработать мобильное приложение, обеспечивающее раннюю диагностику осложнений сахарного диабета.

Материалы и методы. При сопоставлении предлагаемой разработки с существующими аналогами были проанализированы более 30 мобильных приложений, однако ни в одном из них не были обнаружены функции контроля развития поздних осложнений СД. Подана заявка на грантовую поддержку (конкурс УМНИК) с целью реализации разработки программной технологии для контроля осложнений СД.

Результаты. Для решения вопроса несвоевременной диагностики поздних осложнений разрабатывается мобильное приложение с функциями контроля диабета и его осложнений.

Комплекс функциональных возможностей реализуемого проекта:

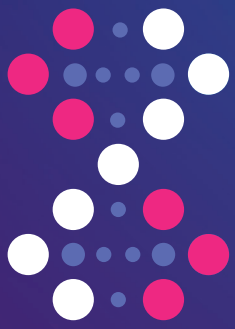
- Контроль гликемии, АД и других показателей.
- Возможность пройти опрос, при помощи которого можно заподозрить то или иное осложнение на ранней стадии.
- «Школа диабета».
- Содержание хлебных единиц в различных продуктах.
- Возможность отправить экстренное уведомление об ухудшении состояния.
- Напоминания о необходимости измерить уровень гликемии и принять лекарственное средство.

Область применения продукта и его потребитель — пациенты, страдающие СД, и врачи по профилям «Эндокринология» и «Терапия».

Выводы. Использование мобильного приложения для скрининга осложнений СД позволит обеспечить раннюю диагностику данных патологических состояний, что приведёт к снижению уровня инвалидизации населения, снижению сроков нетрудоспособности, снижению стоимости терапии осложнений, а также к повышению качества и продолжительности жизни больных.

АВТОРСКИЙ УКАЗАТЕЛЬ

СОДЕРЖАНИЕ



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