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NATIONAL RESEARCH NUCLEAR UNIVERSITY MEPHI
(MOSCOW ENGINEERING PHYSICS INSTITUTE)

The The 6-th International Symposium and Schools for Young Scientists on Physics, Engineering and Technologies for Biomedicine

November 20-24, 2021

PROGRAMME
BOOK OF ABSTRACTS

MOSCOW

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The International Symposium and International School for Young Scientists on «Physics, Engineering and Technologies for BioMedicine» is held annuallyby the Institute PhysBio at MEPhI in Moscow (Russia). The Symposium and Schools aims at bringing together leading scientists, experts, young scientists and students to present their achievements in the format of the invited lectures and poster reports in nuclear medicine, biophysics, bio-photonics, and etc.

Abstracts are published in author's edition

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The 6-th International Symposium and Schools for Young Scientists on Physics, Engineering and Technologies for Biomedicine

The Institute of Engineering Physics for Biomedicine of the National Research Nuclear University (PhysBio MEPhI) announces the International symposium and schools for young scientists and students organized in collaboration with the research centers of the Russian Academy of Sciences, of the Russian Ministry of Health, the State Atomic Energy Corporation and partner universities in Russia and abroad.

The Symposium aims at bringing together the leading researchers, high level engineers and experts in biophysics, bio-photonics, nuclear and nano-medicine to present their recent achievements and to take part in the following discussions.

Two schools for young scientists are scheduled within the Symposium, namely "Physics, Engineering and Technologies for Biomedicine" and "Nanotechnology Approaches for Highly Efficient Production, Detection and Delivery of Bioactive Compounds" which are addressed to students, young scientists and specialists whose activities are related to the life sciences and medicine.

The Symposium and Schools provide an opportunity to obtain knowledge in the latest advances in biomedicine, to exchange opinions and establish professional contacts all over the world. Virtual poster session is planned within the event.

The presentations and lectures embrace the following topics:

- Nanomaterials for biomedical applications
- Bio-photonics for diagnosis and therapy
- Nuclear medicine
- Bioprinting
- Plasma and laser technologies for biomedicine
- Advanced approaches in MRI and PET
- Radiotherapy
- Novel contrast agents for radiation treatment of tumor
- Immunotherapy
- Engineering in translational medicine

Important information

- The Symposium is held on-line via Zoom platform
- Schools are held in-person (with the option of remote connection)
- The official language is English

- Registration is free of charge
- Zoom connection will be provided to the registered participants
- Registration and abstract deadline is November 15, 2021
- Detailed information is available on http://physbio.mephi.ru/symp21/
- Questions can be addressed to Organizers by physbiosymp@mephi.ru

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Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, MEPhI, Moscow, Russia

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The Symposium e-mail: PhysBioSymp@mephi.ru

PROGRAMME
The 6th International Symposium and Schools for Young Scientists on Physics, Engineering and Technologies for Biomedicine

School 1

"Physics Engineering and Technologies for Biomedicine"

November 20, Saturday

09.30	***Opening of the School***
10.00	*Andrei Kabashin* *CNRS (France), MEPhI (Russia)* ***Laser nanofabrication for diverse applications***
11.00	*Anton Fojtik* *Czech Technical University in Prague (Czech Republic), MEPhI (Russia)* ***Nanotechnology approach for sensors, storage energy and genetic information***
11.30	*Vladimir Mironov* *MEPhI (Russia)* ***In-vivo bioprinting***
12.00	*Victor Timoshenko* *MSU, MEPhI (Russia)* ***Silicon based nanoparticles for cancer theranostics applications***
12.30	*Ahmed Al-Kattan* *Aix Marseille University (France)* ***Novel nanoparticles-enhanced biomimetic platforms for medical and tissue engineering applications***
13.00-14.00	***Lunch***
14.00	*Natalia Epstein* *MEPhI (Russia), Obninsk Institute for Nuclear Power Engineering (Russia)* ***The life cycle of medicines and GxP practices***
14.30	*Victor Loschenov* *MEPhI (Russia), Prokhorov General Physics Institute (Russia)* ***Fluorescence diagnostics and photodynamic therapy in the experiment and in the clinic***
15.00	*Vladimir Oleynikov* *MEPhI (Russia), Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, RAS (Russia)* ***Correlative microscopy: state of art and perspectives***

15.30	*Vladimir Morozov* *Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, RAS (Russia)* ***New approaches to the detection of ionizing radiation for biology and medicine***
16.00	*Alexey Lipengolz* *MEPhI (Russia), National Medical Research Center of Oncology N.N. Blokhin (Russia)* ***Neutron capture therapy of malignant tumors***
16.30	*Victoria Shipunova* *MEPhI (Russia), Moscow Institute of Physics and Technology (Russia)* ***Nanostructures for oncotheranostics***
17.00	*Alexander. Kharin* *MEPhI (Russia)* ***Convolutional neural networks for SEM images analysis***
17.30	*Igor Meglinski* *Aston University (UK), MEPhI (Russia)* ***Visual perception of polarized light by humans***
18.00	*Tatiana Savelieva* *Prokhorov General Physics Institute (Russia), MEPhI (Russia)* ***Optical biopsy in neurosurgery***
18.30	*Anton Popov* *MEPhI (Russia)* ***Laser synthesis of colloidal solutions for biomedical applications***
19.00	***Debriefing, discussions, closing of the School***

School 2
"Nanotechnological Approaches to Highly Efficient Production, Detection and Delivery of Biologically Active Compounds"
November 21, Sunday

09.30	***Opening of the School***
10.00	*Yuri Gunko* *Trinity College, Dublin (Ireland)* ***Chiral nanomaterials***
10.30	*Galina Nifontova* *MEPhI (Russia)* ***Stimulus-sensitive delivery systems based on polyelectrolyte microcapsules***
11.00	*Pavel Samokhvalov* *MEPhI (Russia)* ***Colloidal synthesis of nanomaterials for biomedicine, optoelectronics and photocatalysis***
11.30	*Dayana Gulevich* *MEPhI (Russia)* ***Colloidal synthesis code: optimization of reaction conditions by machine learning methods***
12.00	*Victor Krivenkov* *MEPhI (Russia)* ***Two-photon processes in hybrid nanoscale structures for medical diagnostics and optoelectronics***
12.30	*Igor Nabiev* *University of Reims Champagne-Ardenne (France)* ***Control of the functions of biological molecules under conditions of strong light-matter coupling***
13.00-14.00	***Lunch***
14.00	*Andrey Sarychev* *Institute of Theoretical and Applied Electrodynamics, RAS (Russia)* ***The theory of giant raman amplification and new biosensors***

14.30	*Andrey Ivanov* *MEPhI (Russia), Institute of Theoretical and Applied Electrodynamics, RAS (Russia)* ***Amplification of electromagnetic fields by optical metamaterials***
15.00	*Anton Yefimov* *NMIC of Transplantology and Artificial Organs named after V.I. Shumakov (Russia)* ***Scanning probe nanotomography for three-dimensional analysis of nanostructured and hybrid biomaterials***
15.30	*Maria Baryshnikova* *FGBNU «RONC named after N.N. Blochin» (Russia)* ***Nanotechnological approaches to the creation of personalized non-antigenic antitumor vaccines***
16.00	*Maria Sumarokova* *MEPhI (Russia)* ***Mechanical and physico-chemical properties of biomaterials using atomic force microscopy***
16.30	*Konstantin Mochalov* *Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, RAS (Russia)* ***Tunable microresonators for controlling the properties of molecules in the mode of strong light-matter coupling***
17.00	***Debriefing, discussions, closing of the School***

Symposium
"Physics Engineering and Technologies for Biomedicine"
November 22, Monday

10.00	*Sergey Klimentov, Alexander Garmash* *MEPhI (Russia)* ***Greetings from organizers***
10.10	*Andrei Kabashin* *CNRS (France), MEPhI (Russia)* ***Research Agenda in PhysBio MEPhI***
10.50	***KEYNOTE SPEAKER*** *Anton Fojtik* *Czech Technical University in Prague (Czech Republic), MEPhI (Russia)* ***Nanostructures for Biomedical Sensors***
11.30	*Amitava Patra* *Institute of nano science and technology (India)* ***New Possibilities of Metal Clusters for Bio-Applications***
12.00	*Vladimir Fomin* *Institute for Integrative Nanosciences, IFW Dresden (Germany), MEPhI (Russia)* ***Spin-Dependent Phenomena in Semiconductor Micro-and Nanoparticles for Biomedical Applications***
12.30	*Indrajit Roy* *University of Delhi (India)* ***Enzyme-mimetic nanomaterials for light-activated anticancer and antibacterial applications***
13.00-14.00	***Lunch***
14.00	*Viktor Timoshenko* *MSU (Russia), MEPhI (Russia)* ***Nanoparticles for Photohyperthermia Applications***
14.30	***KEYNOTE SPEAKER*** *Irina Zavestovskaya* *MEPhI (Russia), Lebedev Physics Inst. (Russia)* ***Advanced binary nanotechnologies of hadron therapy***

15.10	*Victoria Shipunova* *Inst. of Bioorganic Chemistry of RAS (Russia), Moscow Inst. of Physics and Technology (Russia)* ***Polymer nanocapsules are effective tools for the personified metastatic tumors treatment***
15.40	*Gleb Tselikov* *Moscow Inst. of Physics and Technology (Russia)* ***Transition metal dichalcogenide nanospheres for biomedical theranostics***
16.00	*Victor Krivenkov* *MEPhI (Russia)* ***Bright and stable plasmon-exciton quantum emitters based on semiconductor quantum dots***
16.20	*Ivan Zelepukin* *MEPhI (Russia), Inst. of Bioorganic Chemistry of RAS (Russia)* ***Pharmacokinetics of magnetic nanoparticles in the organism***
16.40-17.10	***Coffee break***
17.10	*Petr Nikitin* *Prokhorov General Physics Institute (Russia)* ***New opportunities for nanobiotechnology, medical diagnostics and food safety control***
17.40	***HONORARY KEYNOTE SPEAKER*** *Paras Prasad* *University at Buffalo (USA), MEPhI (Russia)* ***Neurophotonics and Nanobiotechnology for Brain deseases and disfunction***
18.25	*Anderson Gomes* *Federal University of Pernambuco (Brazil), MEPhI (Russia)* ***Photoacoustic microscopy and tomography with plasmonic nanoparticles***
18.55	*Igor Meglinski* *Aston University (UK), MEPhI (Russia)* ***Mutual interaction of red blood cells influenced by nanoparticles studied by a combined use of optical tweezers and scanning electron microscopy***

November 23, Tuesday

10.00 ***PLENARY LECTURER***
Sergey Deev
Inst. of Bioorganic Chemistry of RAS (Russia)
Hybrid nanostructures for theranostics. Progress, problems, perspectives

10.45 *Deepika Sharma*
Intitute of Nano Science and Technology (India)
Inhibition of heat shock proteins sensitizes glioma cells to magnetic hyperthermia and enhances anti-tumor immune response in xenograft model by abscopal effect

11.15 *Rudolf Steiner*
ILM at Ulm University (Germany)
Tissue diagnostics helps to make medical laser application more save

11.45 *Patricia Alloncle*
Aix Marseille University (France)
Laser-induced cells printing: a versatile tool for applications in biology

12.15 *Victor Tsetlin*
Inst. of Bioorganic Chemistry of RAS (Russia), MEPhI (Russia)
Immunotherapy: autoimmune diseases, envenomation, inflammation and cancer

12.45 *Victoriya Tishchenko*
A.F. Tsyb Medical Radiological Research Centre (Russia)
PSMA-targeted radiopharmaceuticals for imaging and therapy of prostate cancer

13.05-14.05 ***Lunch***

14.05 *Roman Zubarev*
Karolinska Institutet (Sweden)
Orbitrap Fourier Transform Mass Spectrometry redefines chemical mass of hydrogen

14.35 ***KEYNOTE SPEAKER***
Alexander Makarov
Thermo Fischer Scientific (Germany)
Expanding applications of mass spectrometry in modern medicine

15.15	*Igor Nabiev* *Université de Reims Champagne-Ardenne (France), MEPhI (Russia)* ***Label-free detection of SARS-CoV-2 variants of vi-ral protein antigens with sers spectroscopy***
15.45-16.15	***Coffee break***
16.15	***Poster session***

November 24, Wednesday

10.00 ***KEYNOTE SPEAKER***

Marco Durante

GSI Helmholtzzentrum für Schwerionenforschung (Germany)

The future of heavy ion therapy

10.40 *Sergey Polozov*

MEPhI (Russia)

Radiation therapy: new challenges and tasks for Russian accelerator community

11.10 *Alexey Lipengolts, Vsevolod Skribitsky*

MEPhI (Russia), N.N. Blokhin National Medical Research Center of Oncology (Russia)

Radiologic in vivo studies of laser ablated gold nanoparticles in laboratory animals

11.30 *Mikhail Belikhin*

Lebedev Physics Inst. (Russia)

Dosimetric estimation of intrafractional target motion influence on dose distribution in proton therapy using dynamic phantom

11.50 *Vyacheslav Saburov*

A.F. Tsyb Medical Radiological Research Centre (Russia)

The status of the neutron therapy complex based on the NG-24M compact neutron generator

12.10 *Alexander Pryanichnikov*

Lebedev Phycs Inst. (Russia), MSU (Russia)

Possibilities of proton imaging implementation at protom synchrotron: development of irradiation modes with low intensity beams

12.30 *Maxim Kuznetsov*

Lebedev Phycs Inst. (Russia)

Optimization of spatial distribution of irradiation during fractionated proton therapy

12.50-13.50 ***Lunch***

13.50 *Geogry Ermolaev*

Moscow Institute of Physics and Technology (Russia)

Ultimate Phase Engineering with Atomically Thin Transition Metal Dichalcogenides

14.10	*Alexander Kharin* *MEPhI (Russia)* ***Laser ablation of porous silicon targets: a molecular dynamics study***
14.30	*Dmitry Ivanov* *University of Kassel (Germany), MEPhI (Russia)* ***Theoretical Investigation of Metallic Nanoparticles Generation Processes During Pulsed Laser Ablation in Liquids***
14.50	*Martin Garcia* *The University of Kassel (Germany)* ***The SARS-CoV-2 spike protein is vulnerable to moderate electric fields***
15.20-15.50	***Coffee break***
15.50	***Poster session***
20.00	***Discussions and Closing ceremony***

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The 6th International Symposium and Schools for Young Scientists on Physics, Engineering and Technologies for Biomedicine

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The 6th International Symposium and Schools for Young Scientists on Physics, Engineering and Technologies for Biomedicine

INVITED LECTURES

NEUROPHOTONICS AND NANOBIOTECHNOLOGY FOR BRAIN DISEASES AND DYSFUNCTION

Paras N. Prasad
Institute for Lasers, Photonics, and Biophotonics and Department of Chemistry, University at Buffalo, State University of New York, Buffalo, New York 14260, United States
Presenting author e-mail address: pnprasad@buffalo.edu

Brain theranostics, combined diagnostics and therapy, will play a vital role in addressing major challenges the world is facing in dealing with Brian diseases and dysfunction. Brain cancer such as glioblastoma remains a major healthcare problem. Neurocognitive disorders such as Alzheimer's disease, early onset dementia, Parkinson's disease, depression, schizophrenia, and chronic traumatic encephalopathy are major health care issues, which are particularly relevant to the growing aging population. Concussion and chronic traumatic brain injury (TBI) are two ends of the spectrum of clinical brain injury. We are advancing neurophotonics, an emerging field for powerful intervention and remedy to address brain diseases and dysfunctions, which utilizes light for neuron cell-based imaging diagnostics as well as light guided and activated therapies.

For optical imaging of the central nervous system (CNS), we use deep penetrating light in the IR widows of transparency, for which we use nanoformulations that produce *in situ* either IR-to-IR upconversion or down shifting further into IR using rare-earth doped probes. To implement any diagnostic and therapeutic functions in the CNS by crossing the blood brain barrier (BBB), we tailor the nanoparticles and use phantom BBB models to ascertain BBB crossing by using neurophotonics imaging approaches.

For Glioblastoma, we reported donor/acceptor coloaded theranostic photonic nanoparticles TPN-cur/CbV, with curcumin (a safe natural product that can inhibit tumor growth and has light absorption and emission in the visible range) and CbV (fluorescence in the highly tissue-penetrating NIR region) co-encapsulated by Pluronic F-127, which

is known to facilitate BBB crossing of drugs. This TPN-cur/CbV provided image guided therapy, significantly inhibiting tumor growth.

We use optically guided and tracked nanoformulations to treat Alzheimer, as well as optogenetic stimulation and microglia activation to enhance brain function. Our new approach for optogenetic used biocompatible upconversion nanoparticles for on-site optical upconversion to blue light which provided neuronal response on demand leading to a level of precision over signaling events within defined neuronal cell types – crucial to manipulating the biological mechanisms underlying cognitive states. We also used nanoformulations of natural drugs such as ginseng and curcumin to treat Alzheimer. More complex optically activatable nanoformulations made possible by nanochemistry used hierarchically built core-multiple shell nanostructures for optically triggered activation of microglia, resident brain macrophages. In an aging brain, microglia gradually lose their ability for activation to counter brain disease and dysfunction. We developed a yolk-shell structured mesoporous silica coated core-shell upconverting nanoparticles (UCNP@SiO_2), to penetrate BBB, incorporate into the microglia cells and activate them in desired regions of brain in response to NIR illumination

In situ real-time visualization of cerebrovascular dysfunction is vital for the study and treatment of brain injury including ischemic stroke and traumatic brain injury (TBI) which can be caused by an external mechanical force or a shock wave such as from a blast. It can inflict a concomitant injury on the blood vessels, as well as result in impaired regulation of vascular flow and compromise the integrity of BBB. We have developed size selected nanoformulations carrying targeting, imaging and chemotherapeutic agents for spatio-selectrive crossing of BBB region compromised by TBI, for optical image guided delivery of therapeutic agents.

Future perspectives will be presented.

[1] P.N. Prasad, Nanophotonics, John Wiley & Sons, New York, 2004.
[2] P.N. Prasad, Introduction to Biophotonics, John Wiley & Sons, 2003.
[3] P.N. Prasad, Introduction to Nanomedicine and Nanobioengineering, Wiley, 2012.

NOVEL NANOPARTICLE-ENHANCED BIOMIMETIC PLATFORMS FOR MEDICAL AND TISSUE ENGINEERING APPLICATIONS

A. Al-Kattan
Aix Marseille University, CNRS, LP3, 13288 Marseille, France

Brain theranostics, combined diagnostics and therapy, will play a vital role in addressing major challenges the world is facing in dealing with Brian diseases and dysfunction. Brain cancer such as glioblastoma remains a major healthcare problem. Neurocognitive disorders such as Alzheimer's disease, early onset dementia, Parkinson's disease, depression, schizophrenia, and chronic traumatic encephalopathy are major health care issues, which are particularly relevant to the growing aging population. Concussion and chronic traumatic brain injury (TBI) are two ends of the spectrum of clinical brain injury. We are advancing neurophotonics, an emerging field for powerful intervention and remedy to address brain diseases and dysfunctions, which utilizes light for neuron cell-based imaging diagnostics as well as light guided and activated therapies.

The presentation will review novel biomimetic platforms for biomedical applications with particular emphasis on tissue engineering. In particular, it will review platforms based on calcium phosphate apatite as one of most promising materials, as well as present nanoparticles prepared by laser ablation in liquids as a promising functional element for tissue engineering platforms [1,2].

[1] A. Al-Kattan, V. Santran, P. Dufour, J. Dexpert-Ghys, C. Drouet, Novel contributions on luminescent apatite-based colloids intended for medical imaging, Biomaterials Applications, vol. 28, pp. 697-707, 2014.
[2] A. Al-Kattan, S. Girod-Fullana, C. Charvillat, H. Ternetfontebassoa, P. Dufour, J. Dexpert-Ghys, V. Santran, J. Bordere, B. Pipy, J. Bernad, C. Drouet, Biomimetic nanocrystalline apatites: Emerging perspectives in cancer diagnosis and treatment, International Journal of Pharmaceutics, vol. 423, pp. 26-36, 2012.

DOSIMETRIC ESTIMATION OF INTRAFRACTIONAL MOTION INFLUENCE ON DOSE DISTRIBUTION IN PROTON THERAPY USING DYNAMIC PHANTOM

M.A. Belikhin[1,2,3], A.P. Chernyaev[3], A.A. Pryanichnikov[1,2,3], A.E. Shemyakov[1,2]

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[2]Protom ltd., Protvino, Russia
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Intrafractional respiratory-induced motion significantly affects the dose distribution during proton therapy in case of chest and abdomen localizations, and reduces its effectiveness [1]. In this study influence of intrafractional motion during spot scanning proton therapy (SSPT) was estimated using a dynamic phantom for various parameters of motion.

Motion is simulated by the non-anthropomorphic dynamic phantom designed by Protom ltd. Irradiation of the phantom's target was carried out by synchrotron [2]. The PTV has the cube shape of $2\times2\times2$ cm^3 with dose of 5 Gy. The ionization chamber PinPoint 31022 and EBT3 installed in the target were used for dosimetry. The target was moved translationally across the direction of beam propagation. Motion model is based on respiratory-induced motion in free breathing state described by inhale, exhale, pause and amplitude values. Analysis of the dose distributions was carried out in the region of interest (ROI). Result is shown in Table 1, and images of dose distributions are shown in Fig. 1.

Motion induces hot and cold spots with peak 5.9 Gy and 2.3 Gy, respectively (for 10 mm). Homogeneity decreases in proportion to amplitude from 96.7% (static) to 75.5% (for 10 mm). The average dose decreases in proportion to amplitude from 4.9 Gy to 4.1 Gy (for 10 mm) due to distortions and blurring along the motion direction. Homogeneity differs by no more than ±1% for different acceleration cycles and timing parameters.

Intrafractional motion significantly distorts dose distribution when irradiated by proton beam in spot scanning mode. The degree of distortion depends most on the motion amplitude. Thereby, the use of motion compensation techniques is necessary in clinical practice.

Table 1. Result of quantitative analysis of the dose distributions

Cycle, sec	Inhale, sec	Exhale, sec	Pause, sec	Amplitude, mm	ROI dose, Gy	ROI homogeneity, %
2.0	-	-	-	-	4.9	96.7
	1.7	2.0	0.6	2	4.6	95.4
				5	4.5	90.9
				10	4.3	75.5
	1.2	1.4	0.2	2	4.7	95.6
				5	4.5	89.0
				10	4.2	76.4
1.3-1.5	1.7	2.0	0.6	10	4.1	75.9

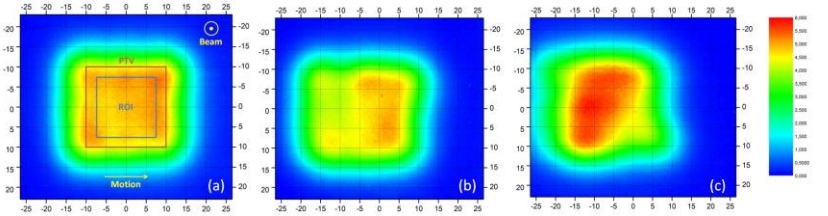

Fig. 1. The dose distributions in static target (a) and in moving target with amplitude of 5 mm (b) and 10 mm (c) built in millimeter coordinate system

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LASER-INDUCED CELLS PRINTING: A VERSATILE TOOL FOR APPLICATIONS IN BIOLOGY

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Printing techniques applied to biology have begun to develop since the 2000s and hold great promise in a near future. They are based on interdisciplinary approaches and use a combination of cells, chemistry, engineering and sophisticated protocols to create artificial tissues.

In that scope, it has been more than a decade since Laser-Induced Forward Transfer (LIFT) is studied in lab scale for its ability to print biomaterials and more specifically living cells [1, 2]. This method uses a short laser pulse to transfer tiny amounts of material from a thin film donor to a receptor substrate. Under appropriate conditions, the pulse induces the formation of a jet propagating perpendicularly to the donor substrate. The targeted material is then deposited as a droplet on the collector (Fig.1a). Due to its nozzle free non-contact direct writing technique, it is considered as a suitable method to print three dimensional cellular structures with a very high spatial resolution. Combined with stem cells technology this innovative printing process opens new perspectives for the creation of complex bio-models strongly mimicking the *in-vivo* environment with numerous applications ranging from regenerative medicine to pharmaceutic study and drugs screening. However, the optimization of its performances and its use with living cells require a deep understanding of the ejection dynamic depending on several laser parameters (laser fluence, repetition rate, laser spot size, laser wavelength, pulse duration, absorption mechanism…) and of the effects of living cells on the bio-ink printability. At LP3 (Marseille-France) and in close collaboration with MMG (Marseille-France), we took ad-

vantages of our expertise in LIFT process [3] to master the printing by LIFT of living cells in good condition (high spatial resolution, high printing resolution and high cellular viability after printing).

Here, we will present the LIFT process and its optimization allowing to master the bio-ink deposition in order to create reliable ordered patterns of bio-ink micro-droplets containing stem cells with a high spatial resolution (Fig.1b) By changing the film concentration in cells and the laser pulse energy, we can control the droplets size and the number of cells per droplet (from tens of cells down to the single cell level). Then, we will present a viability study of the printed cells after transfer to prove the ability of this process to create relevant bio-models.

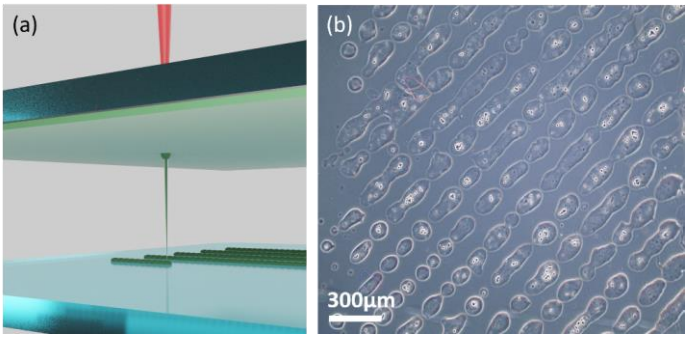

Fig.1. a) Illustration of the LIFT process and b) Lines of polymer embedded of living cells after printing by LIFT

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HYBRID NANOSTRUCTURES FOR THERANOSTICS. PROGRESS, PROBLEMS, PERSPECTIVES

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Theranostics, which is a discipline that combines the diagnosis of malignant tumors and personalized patient therapy, becomes a promising medical strategy for cancer treatment. Theranostic agents perform an accurate diagnostic of molecular targets of pathogenic cells and targeted selective therapy of cancer cells. A lot of theranostic nanoparticles are under investigation and clinical trials now [1-6]. Recent advances in nanobiotechnology have made it possible to design multifunctional structures that combine the functions of recognizing and treating pathological tissues, as well as to monitor therapeutic outcome.

We designed a novel type of theranostic complexes on the basis of upconversion nanoparticles (UCNP) with NaYF4: Yb, Tm composition, in which some of the yttrium atoms were replaced by the beta-emitting isotope 90Y. The nanoparticles were coated with polyethylene glycol, and the recombinant fusion protein DARPin-LoPE, consisting of a targeting peptide with ankyrin repeats (DARPin 9_29, 14 kDa), specifically recognizing the HER2 tumor receptor, and the PE 40 fragment of exotoxin A obtained from Pseudomonas aeruginosa. Combination therapy using the obtained hybrid complex of upconversion nanoparticles with targeted toxin UCNP-RT (R-radioactivity, T-toxin), demonstrated selective cytotoxicity against human breast adenocarcinoma cells overexpressing HER2 receptor and a significant synergistic effect: ~ 2200-fold enhanced toxicity (IC50 = 0.0024 μg / ml), compared to the delivery of any of the toxic agents by themselves [7, 8].

Another type of theranostic agent for combined immuno / chemotherapy was developed by Shipunova, et al. [9]. In this study dual regioselective targeting was performed, which implies the use of two differ-

ent epitopes of the same tumor receptor (in this case, HER2) to target theranostic compounds with different mechanisms of action. We used: (i) PLGA nanoparticles containing a fluorescent dye (Nile Red) and the chemotherapy drug doxorubicin; (ii) a bifunctional genetically engineered immunotoxin DARP-LoPE (42 kDa), consisting of a low immunogenic modification of the therapeutic Pseudomonas exotoxin A (LoPE) and the previously mentioned targeting peptide, DARPin 9_29. In accordance with the proposed strategy, the first chemotherapeutic nanoagent targeted subdomains III and IV of the HER2 receptor using the affibody ZHER2342 (8 kDa), while the second agent, immunotoxin, effectively targeted subdomain I of the same HER2 receptor with the DARPin molecule. It has been demonstrated that dual targeting strategy can enhance the antitumor therapy of HER2-positive cells with a very strong synergistic effect, which made possible a 1000-fold decrease in the effective drug concentration in vitro and a significant improvement of in vivo therapy compared to monotherapy with one of the used drugs. Moreover, this therapeutic combination prevented the grows of metastatic tumor nodules in vivo. Thus, the proposed strategy, using double targeting to the same tumor marker, can be effectively used for treating of aggressive tumors.

After that we implemented a dual targeting therapy based on protein drugs capable of recognizing various antigens on a tumor cell, providing a complementary targeted cytotoxic effect. A combination anti-cancer therapy has been performed with various agents targeting HER2 and EpCAM, tumor antigens overexpressed in breast cancer cells. The combined therapeutic effect was achieved due to two highly toxic proteins - the already mentioned LoPE and ribonuclease of barnase from Bacillus amyloliquefaciens. The delivery of toxins to cancer cells was performed using the anti-HER2 and anti-EpCAM-DARPins targeted polypeptides. We have shown that simultaneous treatment of mammary carcinoma mice with (i) an anti-EpCAM fusion toxin based on LoPE and (ii) HER2-specific liposomes loaded with barnase results in simultaneous elimination of the primary tumor and its metastases. Monotherapy with anti-HER2 or anti-EpCam toxins did not have a comparable effect on metastases [10].

Another promising theranostic approach is pretargeting of tumor receptors, when a non-toxic address agent is first injected in the bloodstream, which recognize pathological cells and binds to their surface, and after that the agent, recognizing addressing molecule with high affinity is administrated. This strategy allows to reduce toxic effects on the normal tissues and enhance targeting of the theranostic agents. This promising technology was demonstrated by two agents, assembled via the Barnase-Barstar protein pair [11]. In this work, barnase connected to the address peptide was used as the first module, and in the second stage, the barstar-conjugated liposomes modified with a powerful toxin were introduced. As a result, we observed a significant suppression of a tumor growth and the complete prevention of the metastases formation.

Application of various multifunctional nanomaterials can enhance therapy due to specific targeting. Nevertheless, a lot of nanomaterials have short blood circulation time due to their rapid recognition by the cells of the mononuclear phagocyte system (MPS). It increases liver and spleen uptake of nanomaterials and reduce their efficiency in vivo. One of the promising methods for prolongation of the blood circulation of nanoparticles modification is the blockade of MPS. This method temporarily reduces macrophage endocytosis in response to the absorption of high doses of low-toxic non-functional material. Various materials were designed for blockade of MPS cells, which significantly improve the delivery of diagnostic and therapeutic agents to target tissues in the organism [12-14].

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SPIN-DEPENDENT PHENOMENA IN SEMICONDUCTOR MICRO- AND NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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This talk represents an overview of spin-dependent phenomena in nonmagnetic semiconductor microparticles (MPs) and nanoparticles (NPs) with interacting nuclear and electron spins [1]. Its goal is to cover a gap between the basic properties of spin behavior in solid-state systems and a tremendous growth of the experimental results on biomedical applications of those particles. I will focus on modern achievements of spin-dependent phenomena in the bulk semiconductors from the theory of optical spin orientation under indirect optical injection of carriers and spins in the bulk crystalline silicon – via numerous insightful findings in the realm of characterization and control through the spin polarization – to the design and verification of nuclear spin hyperpolarization in semiconductor MPs and NPs for magnetic resonance imaging (MRI) diagnostics.

The most common ways to polarize nuclear spins are optical pumping, chemical reaction or direct transfer of spin angular momentum from electron to nuclear spins called dynamic nuclear polarization (DNP). Vividly developing applications of spintronics, in particular, in biomedicine, require a secure control over the spin polarization in semiconductors. The first demonstration of an enhanced DNP was obtained by optical pumping in very pure n-type Si (with the concentration 5×10^{16} m^{-3} of phosphorus atoms, which was much lower than the concentration 2×10^{17} m^{-3} of conduction electrons). Optically induced DNP in semicon-

ductors can be achieved in two ways, using (i) saturation of the electronic spin magnetization with an unpolarized light, which generates an equal number of spins up and spins down and (ii) production of highly polarized conduction electrons by irradiation with circularly polarized light, which generates spin-polarized electrons and holes [2].

Semiconductor MPs and nanoparticles NPs exhibit interesting electronic, optical and magnetic properties, which depend on a preferential orientation of electron and nuclear spins in those particles. These properties are essential for their biomedical applications. Spatial confinement of charge carriers (electron and holes) in a semiconductor nanostructure results in an increase of the spin-lattice relaxation time. Going from itinerant to immobile, fully-localized electrons, while inducing the hyperfine dephasing, can be also beneficial in quenching the spin-lattice relaxation. The dynamic nuclear polarization in semiconductor nano- and microstructures opens fascinating prospects for creation of new efficient contrast agents in MRI, which is a powerful diagnostic tool in biomedicine. Perspective applications of silicon MPs and NPs in hyperpolarized ^{29}Si MRI are discussed. For instance, spin-dependent energy transfer from excitons confined in Si nanocrystals to molecular oxygen in the ground triplet state is promising for application of nc-Si based NPs and MPs in photodynamic therapy of cancer [3].

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THE SARS-COV-2 SPIKE PROTEIN IS VULNERABLE TO MODERATE ELECTRIC FIELDS

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The Spike protein of the SARS-CoV-2 virus can be considered as a smart nanostructure. Most of the ongoing projects aimed at the development of specific therapies and vaccines against COVID-19 use the SARS-CoV-2 spike (S) protein as the main target. The binding of the spike protein with the ACE2 receptor (ACE2) of the host cell constitutes the first and key step for virus entry. During this process, the receptor binding domain (RBD) of the S protein plays an essential role, since it contains the receptor binding motif (RBM), responsible for the docking to the receptor. So far, mostly biochemical methods are being tested in order to prevent binding of the virus to ACE2. Here, we show, with the help of atomistic simulations, that external electric fields of easily achievable and moderate strengths can dramatically destabilize the S protein, inducing long-lasting structural damage [1]. This occurs both for the wild type and the so far known variants of concern (Alpha, Beta, Gamma and Delta). One striking field-induced conformational change occurs at the level of the recognition loop L3 of the RBD where two parallel beta sheets, believed to be responsible for a high affinity to ACE2, undergo a change into an unstructured coil, which exhibits almost no binding possibilities to the ACE2 receptor. Remarkably, while the structural flexibility of S allows the virus to improve its probability of entering the cell, it is also the origin of the surprising vulnerability of S upon application of electric fields of strengths at least two orders of magnitude smaller than those required for damaging most proteins. Our findings suggest the existence of a clean physical method to weaken the SARS-CoV-2 virus without further biochemical processing. Moreover,

the effect could be used for infection prevention purposes and also to develop technologies for in-vitro structural manipulation of S. Since the method is largely unspecific, it can be suitable for application to mutations in S, to other proteins of SARS-CoV-2 and in general to membrane proteins of other virus types.

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ORBITRAP FOURIER TRANSFORM MASS SPECTROMETRY REDEFINES CHEMICAL MASS OF HYDROGEN

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We have developed a new method of stable isotopic ratio analysis in protein samples with amino acid resolution. Analyzing the δ^2H in individual amino acids of proteins extracted from vertebrates, we unexpectedly found in some samples, notably bone collagen from seals, more than twice as much deuterium in proline and hydroxyproline residues than in seawater. This corresponds to at least four times higher δ^2H than in any previously reported biogenic sample. We investigated some of the plausible mechanisms for such anomalous enrichment; however, none of them could explain the observations. The finding puts under question the old dogma that "you are what you eat".

PHOTOACOUSTIC MICROSCOPY AND TOMOGRAPHY WITH PLASMONIC NANOPARTICLES

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Optical imaging modalities beyond optical microscopes for laboratory, pre-clinical and clinical diagnostic have been well exploited and developed due to their inherent characteristics such as non-invasiveness, high spatial resolution, controllable penetration depth and in-vivo real-time capabilities [1]. Among the modern optical imaging modalities, we shall discuss the photoacoustic imaging (PAI) methods [2], which is based upon the light absorption by an endogenous or exogenous medium. The absorbed photons induce a local heating, which in turn creates an expansion/contraction of the affected region with subsequent generation of acoustic waves. Whilst the excitation is done by photons, the detection is performed by acoustic detectors, which opens the flexibility of exciting at different wavelength regimes and detecting with the same acoustic detector. In this talk, we shall review the basics of PAI and give an update review of modern applications. We will concentrate on the use of exogenous nanomaterials as absorbing media for PAI. Besides the well-known gold and silver nanoparticles (NP) [3], Titanium nitride (TiN) NP are a recent class of plasmonic nanomaterials [4] which have been exploited for a myriad of applications, including their use as photothermal agents for cancer therapy and in vivo imaging [5].

We shall describe the use of TiN-NP prepared by a laser ablation technique [4], and their application for photoacoustic microscopy (PAM) and photoacoustic tomography (PAT). We shall explain the role of two-photon absorption and plasmonic enhancement in the image generation process, as exemplified in figure 1 for the PAM setup.

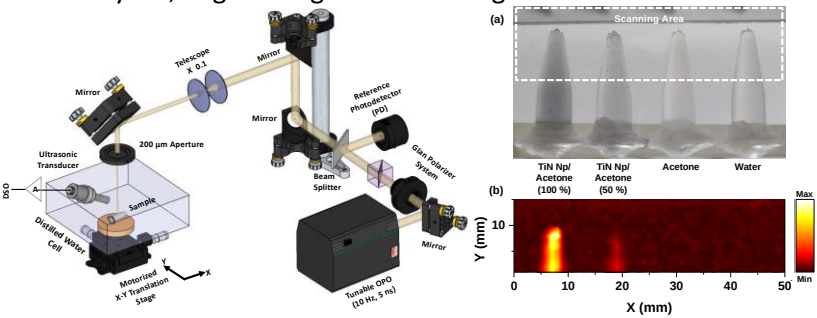

Fig. 1. (Left) experimental setup for PAM; (right) PAM images of TiN NP in an Eppendorf tube

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SYNTHESIS AND STABILIZATION OF $CsPbBr_3$ PEROVSKITES FOR LIGHT EMISSION DIODES APPLICATIONS

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Light emitting diodes (LEDs) due to low power consumption and cost, small sizes, long lifetime, high efficiency and brightness, the ability to emit light of a given color without the use of any color filters found wide application from displays and lighting devices to fiber optics and sensor systems. One of the major component of LED is an electroluminescent semiconductor material such as $A^{III}B^{V}$ (GaN, GaP, GaAs, AlN), $A^{III}B^{VI}$ (ZnSe, CdS, CdSe) or ternary compounds (InGaN, GaAsP, etc.). In the last decade, much attention has been paid to the development of LEDs based on metal halide perovskite nanocrystals (PNCs) with the general formula ABX_3, where A is a monovalent cation (Cs^+, $CH_3NH_3^+$, etc.), B – divalent cation (Pb^{2+}, Ca^{2+}, Ge^{2+}, Sn^{2+}, etc.) and X is a halide or pseudohalide anion. Among the advantages of this class of materials are the bandgap corresponding to visible light mission, low defect emission, high fluorescence efficiency due to the elimination of nonradiative losses and strong light absorption. However, due to specificities of synthesis protocols, upon isolation and purification of colloids, the ligand shell of the nanocrystals readily desorbs, which causes a decrease in colloidal stability and structural integrity of PNCs. Therefore, the aim of this work is the synthesis of $CsPbBr_3$ PNCs and stabilization of their optical properties by post synthetic modification.

$CsPbBr_3$ PNCs were synthesized by the colloidal method using lead bromide and cesium oleate as precursors. The quantum yield of the starting colloid was measured to be 67% relative to fluorescein. Post-

synthetic treatment was carried out in order to rebuild the damaged $PbBr_6$ octahedra and compensate for the loss of ligands after sedimentation/re-dissolution procedure. For this purpose, we have chosen several modificators known in literature to stabilize PNC's surface: dimethyldidodecylammonium bromide (DDAB) in combination with $PbBr_2$, formamidinium bromide (FaBr), and DDAB and FaBr in the mixture with oleic acid (OA). Post synthetic treatment was carried out at room temperature by stirring the calculated amounts of PNCs and modifiers in a toluene solution for 1h. Table 1 summarizes the measured quantum yield, the spectral position of the luminescence peak maximum and full width at half magnitude (FWHM) value.

Table 1. Optical properties of pure $CsPbBr_3$ and modified samples

Sample	modifier composition	λ_{max}, nm	QY, %	PL FWHM, nm
Pure $CsPbBr_3$	–	511	67	19.5
Sample 1	DDAB	512	82	21.4
Sample 2	DDAB + OA	511	81	20.9
Sample 3	FaBr	512	59	20.3
Sample 4	FaBr + OA	513	53	20.3
Sample 5	DDAB + $PbBr_2$	514	95	19.2

According to table 1, treatment by all modifiers containing DDAB lead to a considerable increase in the value of the $CsPbBr_3$ quantum yield. This can be explained by the ability of DDA cations to form a stable ligand monolayer on the surface of PNCs. The most successful attempt was the use of DDAB in combination with $PbBr_2$, which allowed to increase the quantum yield of perovskites from 67 to 95%. Our results pave the way to the enhancement of the stability of PNC colloids, and the improvement of their optical properties, and finally for obtaining high-quality PNC-based LEDs.

This work was supported by the Russian Science Foundation, grant № 18-19-00588-П.

INHIBITION OF HEAT SHOCK PROTEINS SENSITIZES GLIOMA CELLS TO MAGNETIC HYPERTHERMIA AND ENHANCES ANTI-TUMOR IMMUNE RESPONSE IN XENOGRAFT MODEL BY ABSCOPAL EFFECT

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Magnetic hyperthermia therapy (MHCT) has been widely used for the treatment of wide variety of cancer types [1]. However, generation of heat shock proteins (HSPs) following MHCT decreases the efficacy of treatment and thus remain a significant challenge [2]. Therefore, the present work focused on the examination of gene expression after MHCT and using such information to identify target genes that when inhibited could produce an enhanced therapeutic outcome after MHCT. Q-PCR study was performed using glioma cancer cells exposed to MHCT for 30 mins at 43°C, which revealed that HSP 90 expression was upregulated in treated cells as compared to other HSPs. Hence, to enhance the efficacy of the treatment, a combinatorial strategy was employed. In this strategy, 17DMAG was used as an inhibitor of HSPs 90 following the MHCT treatment. The combinatorial therapy resulted in decreased cell viability in 3D tumor spheroids following MHCT + 17DMAG. In vivo tumor regression experiments with MHCT alone and combinatorial MHCT with 17- DMAG on male Wistar rats was performed. A significantly reduction in primary tumor growth rate was observed with combination therapy as compared to controls and MHCT alone. In the group treated with hyperthermia + 17DMAG, the incidence of apoptosis within tumors was greater, and tumor growth was significantly suppressed 28 days in vivo, compared with other treatment groups (Figure 1). The effect of combinatorial therapy was also evaluated on the secondary tumor model, and resulted in robust antitumor effects, known as the abscopal effect. Hence, this work demonstrated that combination of MHCT treatment followed by HSP90 inhibition gener-

ate a synergistic effect and could be a promising target to enhance MHCT therapeutic outcomes in glioblastoma cancer.

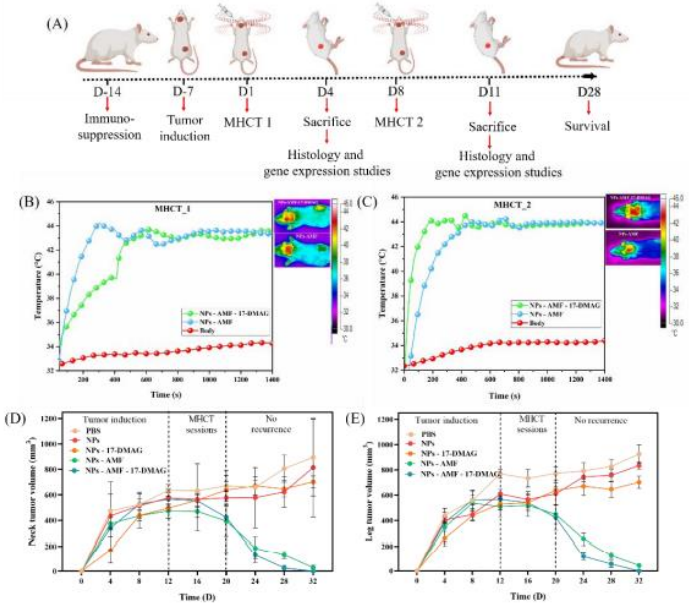

Fig. 1. In vivo MHCT of glioblastomas. (A) Schematic representation of MHCT treatment protocol for tumor eradication. (B and C) Temperature versus time graphs and respective infrared images on (B) MHCT session 1 and (C) MHCT session 2 (335 kHz and 150 Oe) after intra-tumoral injection of MNPs. (D and E) Tumor volume curves during the treatments (n = 6) for (D) primary tumor (neck) and (E) secondary tumor site (leg)

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THEORETICAL INVESTIGATION OF METALLIC NANOPARTICLES GENERATION PROCESSES DURING PULSED LASER ABLATION IN LIQUIDS

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Pulsed Laser Ablation in Liquids (PLAL) has proven itself as a powerful and efficient method of NPs [1] generation for industrial and biomedical applications [2], but due to a number of interrelated processes involved into the laser ablation phenomenon, the final characteristics of the resulting particles are difficult to control. Thus, one of the most important properties of the produced NPs such as their mean size and size distribution, depending on the irradiation parameters, frequently have a broad and multimodal distribution [3]. In this work, we investigate the mechanism of NPs generation in liquids as a function of the pulse duration, the indecent fluence, and the irradiation regime (single- multi-pulse). For that purpose, we applied the combined atomistic-continuum model to simulate ultrashort laser pulse interaction with gold sample under water layer confinement [4]. The model described non-equilibrium laser-induced phase transitions at atomic level and accounts for the effect of free carriers in continuum. The simulation results are directly compared with the experimental data. The preformed study suggests the methodology for generation of NPs due to PLAL with predesigned morphology, size, and size distribution demanded in biomedical applications [5], Fig. 1.

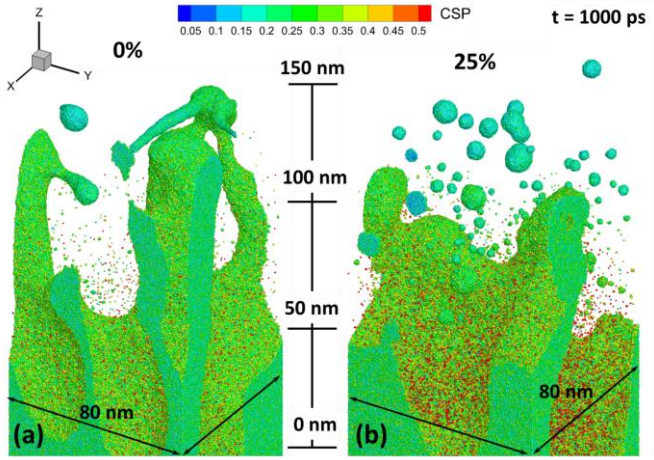

Fig. 1. The atomic snapshots of the irradiated target in water at t =1000ps after the pulse for the initially bulk (a) and porous (b) target. The top 150 nm of the ablating targets are shown for both cases. The water atoms are not shown

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RESEARCH AGENDA IN PHYSBIO MEPHI

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The Institute of Engineering Physics for Biomedicine (PhysBio) was founded in 2016 as one of six new Strategic Academic Units in National Nuclear Research University MEPhI (Moscow Engineering Physics Institute). The establishment of PhysBio was expected to extend the portfolio of MEPhI toward chemical and biochemical research fields, as well as biomedical applications.

This talk will review research agenda in PhysBio MEPHI and present main scientific achievement for last years. The main emphasis will be given to projects implying the synthesis of novel nanomaterials and their applications as contrast agents, sensitizers of therapies, and carriers of radiopharmaceuticals for oncology applications in oncology.

CONVOLUTIONAL NEURAL NETWORKS FOR SEM IMAGES ANALYSIS

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This short message is dedicated to the application of modern deep learning techniques for the analysis of scanning electron microscope (SEM) images. The image processing is an emerged field with huge breakthrough into the recent years. Nevertheless, the application of the most advanced techniques requires a large amount of manually labelled-data. In order to overcome this challenge, a synthetic dataset can be created with the SEM images from [1] used as a textures and a background for round particles. In presented work, it was found that effectiuve neural network training for nanoparticles detection task can be done on the synthetic dataset. We've used a RetinaNet [2] architecture with pretrained for general image recognition task ResNet50 [3] backbone as a NPs detector. The result shows high sensitivity and accuracy of the network for nanoparticles detection on the real SEM images. The created software can help axiomatization of the SEM image processing, particularly creation of the size distribution of the nanoparticles and can be applied for the large-scale image analysis. A result of the algorithm work can be found in the figure 1. A resulted algorithm is set up as free online service.

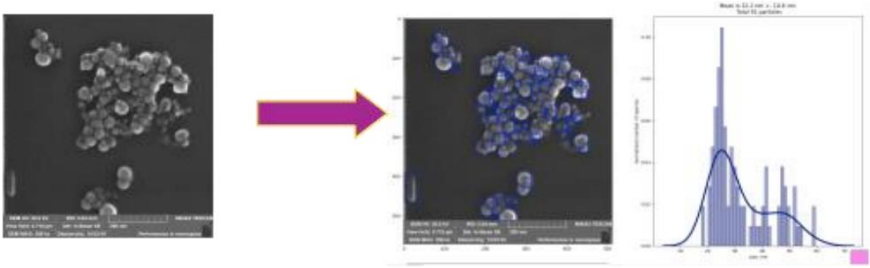

Fig.1. Example of pretrained neural network inference work on typical SEM image

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LASER ABLATION OF POROUS SILICON TARGETS: A MOLECULAR DYNAMICS STUDY

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Laser ablation is one of the rapidly developing and perspective methods for nanofabrication. This method is can be used both for structuring substrates and for the synthesis of nanoparticles with different morphologies. The molecular dynamics simulation models can help the description of some effects presented during laser ablation of solid targets of different morphology.

In the present work, the ablation of a porous silicon target with different pore morphologies has been studied. The number of ablated atoms is calculated for targets with different porosity under irradiation with infrared, visible, and UV spectral ranges with various fluences. The ablation threshold, as well as the ablation rate (expressed as a number of ablated atoms per time unit), were studied as a function of the excitation wavelength and wafer morphology (porosity and average pore sizes). The two major effects were found to significantly affect ablation behavior:

1. A drop of ablation threshold for highly-porous targets. The effect is more pronounced in the case of relatively small pore size (2-3 nm)
2. A drop in ablation efficiency for porous silicon targets, caused by increased porosity and relaxation of internal stress caused by rapid thermal expansion.

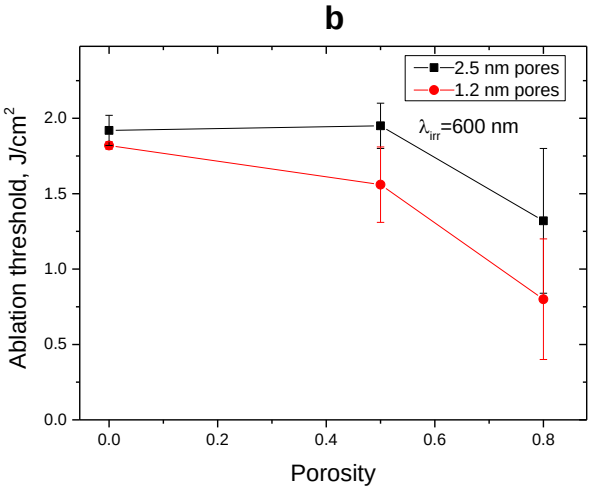

Fig. 1. Calculated dependency of the ablation threshold on porosity of samples

Figure 1 shows the d of the ablation threshold on porosity of samples. The porosity increase leads to the drop of the ablation threshold. The effect is even more pronounced for smaller pore sizes.

Reducing the ablation threshold can be important in the laser ablation synthesis of nanoparticles due to lowering the laser requirements for the ablation.

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BRIGHT AND STABLE PLASMON-EXCITON EMITTERS BASED ON SEMICONDUCTOR QUANTUM DOTS

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Semiconductor quantum dots (QDs) are widely used in medicine [1] and optoelectronics [2] due to very large one- and two-photon absorption cross-sections [3], narrow photoluminescence (PL) spectrum, and high quantum yield (QY) of PL [4]. However, there are still some challenges for the applications of QDs. First is the reduction of their brightness due to the interaction with surrounding media, the other is the temporal instability of their PL known as “PL intermittency” or “PL blinking”. Moreover, the saturation of the single-exciton absorption and very low PL QY of multiexciton states in QDs limit the excitation conditions and overall brightness.

One of the most promising ways to significantly improve the PL properties of QDs and overcome the limitations is their coupling with plasmonic nanoparticles (PNPs). In general, three main effects can be observed when QDs are placed near PNPs – a local enhancement of excitation, acceleration of radiative recombination rate (Purcell effect), and acceleration of nonradiative recombination rate due to the metal-

induced energy transfer. These effects lead to a change in PL QY of excitonic (EX) and biexcitonic (BX) states and to the strong reduction of PL lifetime.

We investigated the EX and BX PL parameters of single QDs in the vicinity of PNPs at different resonance conditions. We found that the excitation is strongly increased in the case of a strong spectral overlap between excitation and PNPs extinction [5, 6]. In the case of strong spectral overlap between QDs PL and PNPs extinction, the radiative rate is increased by orders of magnitude, which leads to an increase of both EX and BX QYs and a near-unity BX-to-EX QY ratio [4]. Moreover, the coupling with PNPs led to the prevention of the temporal instability of the QD PL, probably due to the suppression of the charge transfer. Finally, we managed to combine the excitation enhancement and Purcell effect in one material with a synergistically increased PL intensity, ultrashort PL lifetime, and sufficiently increased BX QY [5, 7].

Here we summarized the results, which open new ways for the practical application of the QD-based plasmon-exciton quantum emitters, particularly for the fabrication of the highly efficient quantum emitters, fluorescent biomarkers, and light-emitting surfaces.

This study was supported by the Russian Science Foundation, grant no. 18-72-10143-П. V. K. has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie, grant agreement no. 101025664 (QESPEM).

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OPTIMIZATION OF SPATIAL DISTRIBUTION OF IRRADIATION DURING FRACTIONATED PROTON THERAPY

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Approximately half of the patients, diagnosed with cancer, undergo radiotherapy. Most often irradiation is delivered via beams, which source is external to the patient. Radiation affects not only cancer cells, but normal tissues as well. One option to reduce normal tissue damage is to concentrate the radiation dose within the tumor mass. Due to the specific features of different types of irradiation, for traditional X-ray radiotherapy this task can be solved with quite limited efficiency, while the use of protons can allow to target desired regions much more precisely with less radiation delivered to surrounding healthy tissue.

Normal tissue damage can also be reduced by proper fractionation of total dose, i.e., its division it into much smaller fractions, administered over a period of several weeks. Fractionation also allows to get advantage of the spatiotemporal effects that are widely referred to as the four R's of radiotherapy. The first effect is the repopulation of tumor cells that takes place between the irradiations. The second effect is the repair of sublethal damage, which can generally be neglected, unless the time interval between irradiations is as short as several hours. Two remaining effects – reoxygenation and redistribution of cell cycle – indicate that the radiosensitivity of a cell depends on the surrounding concentration of oxygen and on the current stage of its cell cycle. In particular, hypoxic and non-proliferating cells are more radioresistant.

In practice, during proton therapy tumor volume is uniformly irradiated. However, due to the diffusional limitation of nutrient supply from the microvasculature, the growing tumor has non-uniform radiosensitivity of its cells. This fact can be taken advantage of during proton ra-

diotherapy via optimization of spatial distribution of irradiation within the tumor, that would increase the number of killed tumor cells and therefore the chances of tumor cure, keeping the normal tissue damage at preassigned tolerable level. In this work the theoretical potential of such spatial optimization is discussed along with its pitfalls and the possibility of using in practice.

The study was funded by RFBR according to the research project № 19-01-00768 and by the Ministry of Science and Higher Education of the Russian Federation, subsiding agreement no. 075-15-2021-1347.

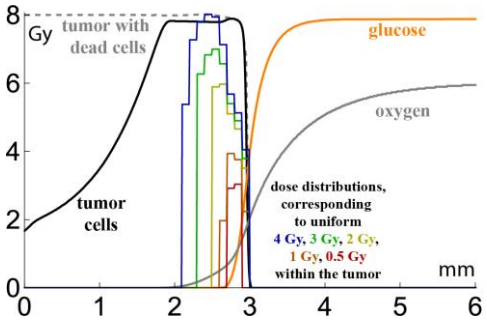

Fig.1. Optimized spatial distributions of proton irradiation, leading to greater number of dead tumor cells under the same damage to normal tissue, as uniform dose distributions within tumor would cause

Table 1. Comparison of efficiencies of single proton irradiations, uniform within the tumor, and proton irradiations with optimized spatial distributions, causing the same damage to normal tissue

Uniform dose within the tumor	Dead cells, uniform dose distribution	Dead cells, optimized dose distribution	Ratio of dead cells under optimized and uniform dose distributions
0.5 Gy	$1{,}56 \cdot 10^6$	$3{,}59 \cdot 10^6$	2.30
1 Gy	$3{,}23 \cdot 10^6$	$6{,}05 \cdot 10^6$	1.87
2 Gy	$6{,}65 \cdot 10^6$	$9{,}70 \cdot 10^6$	1.46
3 Gy	$9{,}89 \cdot 10^6$	$1{,}26 \cdot 10^7$	1.27
4 Gy	$1{,}27 \cdot 10^7$	$1{,}50 \cdot 10^7$	1.18

LABEL-FREE DETECTION OF SARS-CoV-2 VARIANTS OF VIRAL PROTEIN ANTIGENS WITH SERS SPECTROSCOPY

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The emergence of the SARS-CoV-2 betacoronavirus, the pathogen of COVID-19, is an urgent threat to human health worldwide. The 2020 global world pandemic situation could have been prevented had a large-scale, quick diagnosis of active infection cases been possible, which further confirms that more efficient methods for detecting and controlling viral infections are to be developed. The main component of SARS-CoV-2 spikes, spike glycoprotein (S glycoprotein), which is responsible for recognizing the host cell receptor and entering the host cell, is the main target of both diagnosis of coronavirus infection and the vaccines to be developed against it. The development of a highly sensitive and specific spectral method of quick detection of S glycoprotein would ensure earlier diagnosis of SARS-CoV-2 infection.

Surface-enhanced Raman scattering (SERS) spectroscopy is a surface- or cavity-enhanced variant of Raman scattering spectroscopy allowing the detection of analytes with a sensitivity down to single molecules. The main prerequisite for the effectiveness of this method is the development of SERS-active surfaces or cavities capable of concentrating incident radiation into small mode volumes containing the analyte.

Here, we have demonstrated that concentration of light in an ultranarrow metal–dielectric nano-cavity between a film of the SARS-CoV-2 viral protein antigens and silver surface, which were formed via interaction of sulfhydryl groups of the viral antigens with silver, allows recording SERS spectra at concentrations sufficient for ultrasensitive

detection of SARS-CoV-2 at physiologically relevant (sub-picogram) levels (Figure 1). Our study is the first to obtain characteristic Raman and SERS spectra of the key SARS-CoV-2 viral antigens directly, without the use of low-molecular-weight Raman-reporter molecules. The possibility of direct recording of characteristic spectra of viral protein antigens at the concentration orders of magnitude lower than those required for the detection of the whole virus in biological media makes the development of a high-performance optical method for detecting and analyzing the pathogen variants a realistic task.

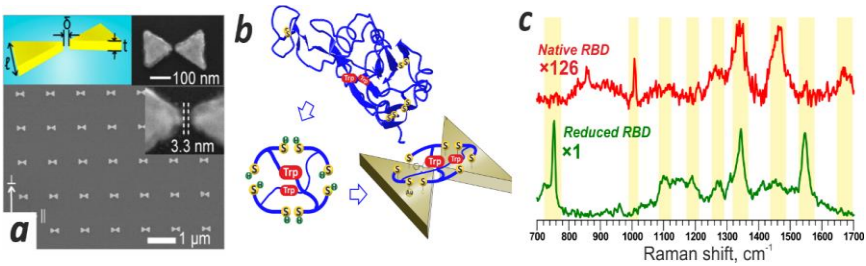

Fig. 1. Concept sketch demonstrating SERS-based detection of the receptor-binding domain (RBD) of SARS-Cov2 spike-glycoprotein (S-GP) or entire viruses. Here, the plasmonic bowtie nanoantennae (a) is used to detect and study RBD (b) or whole deactivated viruses (c) in their native form or after reduction of proteins' S-S bonds for release of free thiol groups with high affinity to SERS-active surface, an approach which what approved by us in [1]. The SERS-spectra of the key viral protein antigen shown in (c) were recorded at the concentration orders of magnitude lower than those required for the detection of the whole virus in biological media

This work was supported by the "Viruses" Call of the Russian Foundation for Basic Research, grant no. 20-04-60440.

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NEW OPPORTUNITIES FOR NANOBIOTECHNOLOGY, MEDICAL DIAGNOSTICS AND FOOD SAFETY CONTROL

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Several ultrasensitive optical and magnetic methods have been developed for nanobiotechnology and tested as the metrological tools for theranostics applications, medical diagnostics, food safety control, etc.

Based on the developed hybrid nanoparticles (NP) and their quantification methods, new results are obtained for NP accumulation in various tissues and tumors, as well as for a significant enhancement of the nanoagents delivery to cancer tumors in animals *in vivo* [1].

In the experiments, the magnetic drug nanocarriers were mainly used because they can be noninvasively quantified in organs of animals by nonlinear magnetization with a new generation of the readers [1,2].

The nanoagents hold great potential for biomedicine as they outperform molecular agents *in vitro.* However, most of the promising nanoagents become theranostically inefficient *in vivo* because of rapid elimination from the bloodstream by the mononuclear phagocyte system (MPS). We have developed a universal method for increasing the circulation half-life of the nanoagents by preceding stimulation of the MPS clearance of the organism's own intact blood cells [1]. We show that administration of a minute dose of allogeneic anti-red blood cell antibody that induces a temporary "MPS-cytoblockade" provides up to 32-fold increase in nanoagent circulation half-life and accumulation in the tumors. The proposed method of MPS blocking significantly improves the efficiency of various nanotherapeutics.

The synthesized nanoparticles conjugated with biorecognition molecules were also used for development of rapid formats of *in vitro* immuno- and DNA assays. In particular, a new ultrasensitive method was developed for direct (without any amplification of reaction) measuring the concentration and identification of RNA / DNA molecules based on a combination of RNA and gold nanoparticles. The record sensitivity up to 30 fM was achieved for DNA concentration in a small sample volume of 20 μl with a rapid (15 min) and easy-to-perform assay [3]. That is promising for novel tools for diagnosing diseases.

Highly sensitive optical methods were developed for differential diagnosis of autoimmune diseases based on the spectral-correlation interferometry [4] and image processing of a microarray glass sensor chip. New criteria in comprehensive diagnostics of autoimmune diseases were proposed for the first time based not only on traditional measurements of concentration of autoantibodies, but also on quantitative evaluation of autoantibody aggressiveness to the organism's tissues [4].

The proposed instruments were also adapted and tested for biosensing and food safety control. In particular, the developed readers with sensor chips coated with a graphene layer functionalized with aptamers were used for detection of mycotoxins (ochratoxin A) in food [5].

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LASER SYNTHESIS OF NANOMATERIAL FOR BIOMEDICINE

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Laser ablation in liquids is a relatively simple physical method for the synthesis of colloidal solutions of nanoparticles (NPs). This method offers a unique level of purity of the synthesized nanomaterials. Laser ablation in liquids was developed in the last decade of the twentieth century [1] and is currently used for synthesis of wide range of nanomaterials applied in diverse applications, including biomedicine [2]. Laser ablation is based on a natural production of nanoclusters during the action of laser radiation on a solid target. Laser ablation does not require specific chemicals for synthesis, which makes it possible to ensure that any residual contamination of the NP surface is avoided. The lecture outlines the basics of laser ablation in a liquid: the main physicochemical processes occurring during the formation of NPs, the structure of the experimental setup, methods of controlling the parameters of the resulting NPs.

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POSSIBILITIES OF PROTON IMAGING IMPLEMENTATION AT PROTOM SYNCHROTRON: DEVELOPMENT OF IRRADIATION MODES WITH LOW INTENSITY BEAMS

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The development of accelerator technologies in recent decades has made it possible to actively use proton therapy in clinical conditions [1]. The current paradigm of proton therapy is the use of conditional X-ray computed tomography for future proton therapy irradiation procedures. However, it is necessary to know the relative stopping power of protons for each voxel of the volume of interest in order to plan the irradiation. The calculation of proton relative stopping power is based on the conversion of Hounsfield CT units for the patient's tissues [2]. Uncertainties in this conversion leads to larger proximal and distal planned target volume margins [3]. These larger margins increase the dose to nearby healthy tissues, causing unwanted toxicities. Proton imaging avoids these uncertainties by directly measuring proton stopping power, and this can reduce the planned target volume, thus directly reducing toxicity [4].

Protom Synchrotron is a medical accelerator specially designed for proton therapy. The synchrotron is able to accelerate protons up to 330 MeV [5-6]. This fact makes proton imaging of the entire human body available without any restrictions. The use of proton imaging will allow us to avoid the uncertainty of the proton range in the patient's body and will make the treatment process more accurate. Moreover, proton radiography can be used as a tool for verification of patient position instead of standard cone beam computed tomography systems.

The proton imaging system has a lower equivalent dose to the patient than comparable X-ray imaging systems. However, proton imaging systems cannot handle the proton beam intensities used in standard proton therapy.

This means that for implementation of proton imaging it is necessary to reduce the intensity of the protons significantly [7].

To implement low intensity beam extraction, the following actions were performed: a decrease in the number of injected protons, modification of beam extraction mode for the accelerator, development of the extracted beam control and feedback system, development procedures for calibration and verification of extracted proton beams. Calibration procedures and measurements were performed with certified Protom Faraday Cup, PTW Bragg Peak Chamber and specially designed experimental photomultiplier detector [8].

The study made it possible to achieve the values of the extracted beam intensity required for the implementation of proton imaging mode.

The development can be implemented in any proton therapy complexes based on the Protom synchrotron. This allow us to use initial synchrotron beam as a tool for patient verification and to eliminate proton range uncertainties.

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ENZYME-MIMETIC NANOMATERIALS FOR LIGHT-ACTIVATED ANTICANCER AND ANTIBACTERIAL APPLICATIONS

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The ability of some nanomaterials to duplicate the activity of certain enzymes paves the way for several attractive biomedical applications, which bolsters the already impressive arsenal of nanomaterials to combat deadly diseases. The 'enzyme-mimetic' nanomaterials can further be loaded with active agents for synergistic action. A key feature of these nanomaterials is to modulate the oxidative balance of treated cells for facilitating a particular biological process, such as cellular apoptosis. Recently, our laboratory has actively investigated Prussian blue and its analogues, as well as iron-containing nanoparticles that not only show enzymatic activity, but also robust visible-NIR light-absorption and subsequent hyperthermia. We have explored the combination of oxidative modulation and photoactivated hyperthermia induced by a single nanoparticle for the treatment of cancer and bacterial cells. We have observed that such a synergistic therapy can by-pass the various defense mechanisms adapted by rogue cells, such as hypoxia, drug-rejection, etc. The effect of these nanomaterial-induced therapies on cancer and bacterial cells, as well as the future prospects of these therapies, shall be included in this presentation.

PROBING THE INTERACTIONS BETWEEN NANOPARTICLES AND CELLS

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In the past decades, functionalized nanoparticles have attracted great attention in biomedical research and been widely used in bioimaging, biosensing and theranostics. However, up to date, there has been very few formulations successful in clinical practices. Among all nanomaterials, inorganic nanoparticles, such as metallic nanoparticles, quantum dots, carbon nanomaterials and various 2-D nanomaterials, have demonstrated outstanding physicochemical properties, which be beneficial in biomedical applications. Recent reports have shown their great potential in targeted imaging, tracking, drug delivery and therapy. However, none of these have passed FDA restrictions for clinics. One of the most discussed hurdles is their potential risk when introduced in vivo. However, their advantages lie, yet the accumulation in the major organs and the unclear long-term route of the nanoparticles have greatly discouraged the clinicians. To sort out this problem, one should thoroughly and carefully examine the interactions between the nanoparticles and the biological system in details. In this contribution, we would like to introduce the recent developments in nanoparticle design and the efforts made in understanding the interactions between them and the biological system, down to the subcellular level. In this presentation, gold nanorods have been used as a model nanoparticle to probe the interactions between nanoparticle and the mouse macrophages. Owning to the inert chemical property, gold nanorods are not easily degraded after been internalized into macrophages. Due to the localized surface plasmon resonance, the gold nanorods could be easily tracked through dark-field imaging and colocalized with subcellular organelles through fluorescent imaging. Through tracking and imaging, we found that the functional-

ized gold nanorods were transferred from endosomes to lysosomes and excreted through exocytosis. Also, the cell cycle of the macrophage was arrested at different stages for nanoparticle with different surface modifications. Further investigation has shown that the surface modification of the nanorods could alter the interactions between the nanoparticles and the proteins and lead to different results. These findings would provide some details on the nanoparticle–cell interactions and help us to get a better understanding on this issue.

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OPTICAL BIOPSY IN NEUROSURGERY

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One of the important areas of neurosurgery is the removal of intracranial tumors. Moreover, some of them are characterized by diffuse growth in healthy tissue, which makes it difficult to determine their boundaries. In recent years, video fluorescence analysis of the accumulation of a tumor marker 5-ALA induced Protoporphyrin IX in tissues has been increasingly used to solve this problem. However, the surgeon's perception of a fluorescent image is subjective, which affects the radicality of tumor removal with fluorescence guidance. We propose a quantitative approach to the analysis of the concentration of a fluorescent marker based on fluorescence spectroscopy, supplemented by diffuse reflectance spectroscopy. At the same time, for non-fluorescent gliomas, we proposed a method for analyzing the molecular composition of tumors based on Raman spectroscopy. Taken together, these methods provide sufficient information for tissue identification, which allows this approach to be called optical biopsy.

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NANOSTRUCTURES FOR ONCOTHERANOSTICS

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More than twenty nanoparticle-based drugs are already used in clinical practice for the treatment of cancer, and a number of compounds are in the final phases of clinical trials. The effectiveness of these drugs, for example, the liposomal form of doxorubicin (Myocet, Kelix) or the micellar form of paclitaxel (Genexol-RM), is based on the effect of enhanced permeability and retention of tumor vessels (EPR effect, enhanced permeability and retention effect). However, the EPR effect is very heterogeneous even within a single tumor and is much more pronounced in rodents than in real human tumors. This is mainly due to a lower tumor growth rate in humans and the formation of a normal vascular network with developed lymph drainage compared to rapidly proliferating rodent tumors. Moreover, even in cases of a really strong EPR effect (for example, with rapidly developing Kaposi's sarcoma), only a small percentage of the total administered dose of nanoparticles (less than 0.7%) reaches the tumor area.

The report presents a series of works directed toward the development of nanostructures of various nature, the most effective for the treatment of large solid tumors (magnetic, gold, silver, protein, silicon, hybrid smart structures, as well as polymer) [1-15]. Original approaches to the circulation of nanoparticles prolongation in the bloodstream and increasing their diagnostic and therapeutic efficacy are described. This study is a step towards creating a new generation of biomedical tools capable of disease diagnosing and acting as a therapeutic compound when needed.

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POLYMER NANOCAPSULES ARE EFFECTIVE TOOLS FOR THE PERSONIFIED METASTATIC TUMORS TREATMENT

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In recent decades, significant progress has been achieved in the development of targeted drug delivery systems for oncotherapy. However, the successful diagnosis and treatment of cancer is still a serious problem due to the lack of specificity, high required doses of drugs, and the insufficient number of molecular targets on the cell surface. Nanoparticles of different nature are the most promising tools for the development of next-generation targeted drugs [1-15].

In particular, polymer nanoparticles from biodegradable substances are probably the most promising matrix for the delivery of cytotoxic and cytostatic drugs to tumor cells. Here we describe the series of studies directed toward the development of PLGA-based photodynamic and photothermic methods on metastatic cancer treatment. PLGA, or poly(lactic-co-glycolic acid), is a copolymer of lactic and glycolic acid which are presented in the human organism thus proving the biocompatibility of PLGA as the main building block for nanoparticle synthesis.

PLGA nanoparticles of 140 nm were synthesized and loaded with different photodynamic and photothermic sensitizers in order to produce light-induced cancer cell death. To specifically deliver as-obtained nanoparticles *in vitro* and *in vivo* to HER2-overexpressing cancer cells, their surface was modified with anti-HER2 protein scaffolds, DARPins, and affibody – small proteins of non-IgG origin mimicking IgG activity in target recognition without any specific immunomodulation.

The targeted PLGA particles were successfully used for the therapy of solid metastatic tumors overexpressing HER2 – a well-known tumor marker which overexpression often correlates with poor prognosis for

patients. We showed that using the designed approaches the full tumor remission is achievable, even in the case of metastatic tumors treatment. The developed targeted carriers directed toward HER2 oncomarker and loaded with targeting, imaging and diagnostic modalities can give rise to the development of the "magic bullet" concept and bring up the quality of personified medicine to a new level.

The research was supported in part by the Russian Science Foundation grant (project No. 17-74-20146, nanoparticle synthesis, *in vivo* studies) and Russian Foundation for Basic Research (project No. 19-29-04012, cell culture and No. 20-34-70136, plasmonic particle characterization).

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RADIOLOGIC *IN VIVO* STUDIES OF LASER ABLATED GOLD NANOPARTICLES IN LABORATORY ANIMALS

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Nowadays contrast-enhanced radiotherapy is developed as a way of improving efficacy of conventional radiotherapy. Gold nanoparticles can serve as dose-enhancing agent, because gold has a high atomic charge (Z=79) [1-3] and is biocompatible material. The laser ablation method of nanoparticles synthesis is more profitable for biomedical application [4]. The goal of this study was to synthesize biocompatible laser-ablated gold nanoparticles and to study its distribution *in vivo*.

As a result, the colloidal solution of gold nanoparticles was synthesized with femtosecond laser ablation method. Gold nanoparticles were coated with polymer SH-PEG 2 kDa and were concentrated by evaporation of the liquid phase solution up to 85 (mg Au)/cc. The average core diameter and mode of hydrodynamic diameter was 9 nm and 19 nm, respectively.

The biodistribution study was performed on female mice C57Bl/6 with transplanted murine mammary carcinoma Ca755 with microCT method. Colloidal solution of gold nanoparticles was injected via tail vein in volume of 0.2 mL. As a result, gold nanoparticles have a long blood circulation time up to 24 h. Effective accumulation and retention at 20-60 min after injection in the experimental carcinoma Ca755 (fig. 1) was also proved. This accumulation time is enough for radiotherapy. In conclusion, synthesized and studied gold nanoparticles can be a potential base for creation of dose enhancing agent for contrast enhanced radiotherapy.

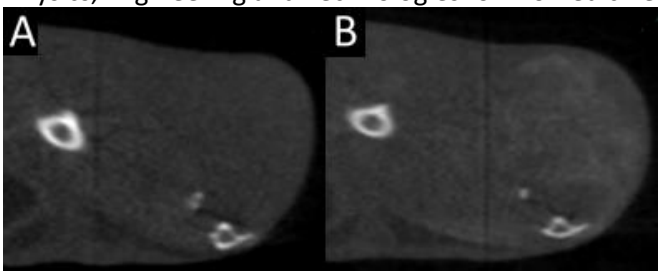

Fig.1. Axial microCT images of experimental Ca755 before (A) and in 30 min after (B) intravenous injection of gold nanoparticles

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TISSUE DIAGNOSTICS HELPS TO MAKE MEDICAL LASER APPLICATION MORE SAVE

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Tissue diagnostics has been notably improved during the last decades. Essential optical parameters used are absorption, scattering, fluorescence of the tissue, auto- or xenofluorescence, specific wavelength of the exciting laser light and coherence conditions. Such basic laser-tissue interactions can be used to control therapeutic laser applications. Some examples include applications in ophthalmology, urology and dentistry.

The first therapeutic laser application at all was the use of a Nd:YAG laser to coagulate the retina after retinal detachment. But the conditions to find the right laser parameters are different from patient to patient due to individual differences in absorption and scattering. Therefore, the doctor has to titrate laser power to get the right retinal coagulation. Automatic online feedback of laser tissue interaction would be of tremendous help. This can be realized taking into account online diagnostics to control the laser reaction.

Pulsed laser applications to disintegrate stones in urology started about 30 years ago but did not become routine. Now, with the development of powerful pulsed Holmium lasers, the situation changed and the lasers are used in prostate ablation and stone disaggregation. But it might be dangerous, when the laser missed the stone and hits soft tissue. Here, online detection of stone fluorescence helps, to control and stop laser interation, when the beam does not hit the stone to be destroyed.

Also in dentistry there is the possibility to detect caries or periodontic plaques by autofluorescence and to control laser treatment. Not the spectral condition will be the solution but the fluorescence contrast between carious and sound hard tissue is a precise measure to control laser applications.

MECHANICAL PROPERTIES OF BIOMIMETIC PROTEIN FILMS BY USING AFM

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Design of biocompatible biomimetic materials and protein-based films requires understanding of the mechanisms of protein adsorption. A main bottleneck related to the adsorption of proteins is their possible denaturation and function lose. This problem should be solved if the films retaining the original proteins function for further biomedical and biotechnological applications need to be engineered.

Two proteins with distinct biological functions are proven to be interesting for films engineering. The fibronectin (FN) is involved in cell adhesion, growth, and migration; the FN thin films are extensively employed in cell attachment experiments. The mucin (MUC) is the main component of mucus secretion. Precise description of its role is complicated because pure MUC difficult to isolate and require the use of methods which may change the protein's structure and function. Properties of the MUC varies with the pH and ionic strength.

Here, we have used a Force Spectroscopy mode of Atomic Force Microscopy (AFM) approach to determine the adhesion forces and unfolding of FN films under the protein non-specific interactions. We have also investigated the mechanical properties of MUC under specific interactions. For both cases measurements were performed by varying loading rate and dwell time and the environmental conditions for the MUC films.

In particular, the results for FN showed that their adhesion and mechanical properties depend on dwell time and loading rate. Applied loads of 2 nN were able to stretch the FN layer up to 200 nm and to un-

fold the three FN domains: FN I (13.5 nm), FN II (18 nm) and FN III (27 nm) (Figure 1) [1]. Furthermore, the adhesive behavior of MUC varied mainly with pH value and also with dwell time and loading rate when exposed to hydrophilic AFM-tips. The largest adhesion values and higher wettability were found for pH 4 (when compared with pH7). Cell-mucin films interactions were enhanced when for MUC films treated with pH4.

This work demonstrated that adhesion force related to a non-specific interaction between a silicon nitride cantilever and FN-film depends on the dwell time and loading rate. The identification of FN domains and related changes caused by pH wetting properties of MUC-films were detected by the chemical force spectroscopy and Wilhelmy plate measurements and confirmed by additional cell adhesion and proliferation study.

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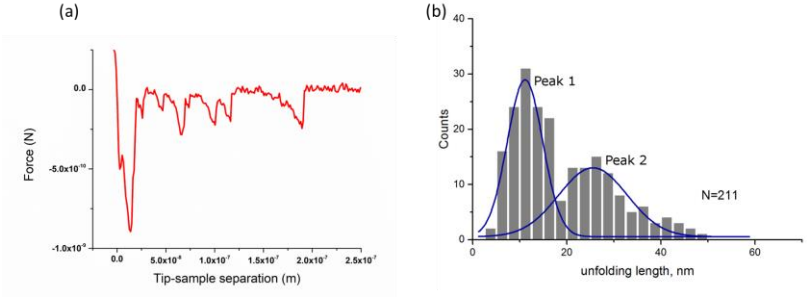

Fig.1. (a) An example of force-distance curves observed for the retract segment: adhesion peak followed by multiple rupture events, that might correspond to the unfolding of FN domains. (b) A histogram showing the unfolding length of FN at dwell time 1s and loading rate 1μm s^{-1} for N=211 analyzed events. The fitting shows the peaks at 11.38±0.45 nm and 25.54±1.65 nm which correspond to the lengths of the FN I and FN III domains

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PSMA-TARGETED RADIOPHARMACEUTICALS FOR IMAGING AND THERAPY OF PROSTATE CANCER

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Prostate cancer is the second most common malignancy and fifth leading cause of cancer death among men worldwide in 2020 [1]. Moreover, it is predicted the increasing of cancer burden up to 2.3 million cases to 2040 [2]. High mortality of prostate cancer is much related to metastasis development. So systemic administration of radiopharmaceuticals is the best approach for diagnostics and therapy of advanced prostate cancer. In this case both primary and metastatic tumors are selective delivered high radiation doses.

Prostate-specific membrane antigen (PSMA) is a non-secreted membrane glycoprotein containing 750 amino acids. PSMA is highly expressed by almost all histological types of prostate cancer (up to 1000 times higher than normal prostate cells), especially in metastatic, low differentiated and castration-resistant cancer. Additionally, PSMA are shown in neovasculature of several other solid tumors, such as breast cancer, renal cancer, etc [3]. So PSMA is an ideal target of prostate cancer for the delivery of diagnostic or therapeutic agents.

Many radioligands targeting PSMA have been created and introduced in routine clinical practice during the last three decades. Among them are various monoclonal antibodies and their fragments, urea-based low molecular weight inhibitors, RNA aptamers [4]. A lot of clinical studies demonstrated high efficacy and low toxicity of PSMA-targeted radioligands in imaging and therapy of prostate cancer. Unfortunately, in Russia PSMA-based radioligand imaging and therapy is nearly not

available, and there are no registered PSMA-targeted radiopharmaceuticals.

In this review the current state of PSMA targeting in prostate cancer diagnostics and treatment will be discussed. Also the results of our study for development of PSMA-targeting radiolabeled agent for prostate cancer treatment will be presented.

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THE INFLUENCE OF PARTICLE SIZE ON PHARMACOKINETIC PROPERTIES OF 103Pd-ALBUMIN MICROSPHERES

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Radionuclide therapy is one of the most convenient method of cancer treatment. Human serum albumin microspheres (HSA) labeled with ^{99m}Tc have a lot of clinical applications, such as studying of regional blood flow in lungs or cardiac function tests [1]. HSA are characterized by high biocompatibility and biodegradation, so they are considered to be useful for radiopharmaceutical development. Palladium-103 (^{103}Pd) has appropriate properties ($T_{1/2}$ = 17 h, Eγ = 21 keV) for prostate and eye cancer brachytherapy [2, 3]. HSA can serve as vehicle for selective delivery of ^{103}Pd and has to guarantee long-term activity retention at target site. The aim of this work was to investigate the biodistribution of ^{103}Pd-HSA (5-10 and 20-40 μm) after intramuscular and intratumoral administration.

HSA was prepared by thermal denaturation (at 150 °C) of protein in olive oil at continuous stirring. Fractionation was performed with sieves. HSA microspheres were dried in a vacuum box at 100 °C and 0.1 mm Hg for 1 h. ^{103}Pd with carrier ($PdCl_2$) was used to prepare ^{103}Pd-HSA by ionic sorption. Reduction of $PdCl_2$ in HSA was carried out with $Na_2S_2O_4$. Injection forms of ^{103}Pd-HSA were prepared as follows: ^{103}Pd-HSA was suspended in 0.1 % of Tween solution in 0.9 % NaCl.

All animal studies were carried out in intact outbred mice and mice with subcutaneously transplanted Echrlich carcinoma. Intact mice were administrated into femur muscle with ^{103}Pd-HSA (0.185 MBq/mouse) in a volume of 0.1 ml. At 7 days after tumor transplantation mice with tumor were also injected in tumor with ^{103}Pd-HSA (0.185 MBq/mouse) in a volume of 0.1 ml. At 5 min, 3 h, 1, 3, 5, 10, 20 and 40 days after ^{103}Pd-HSA administration animals were sacrificed by cervical disruption. The samples of different organs and tissues were collected, and the radioactivity was measured

using automatic gamma counter. The values were expressed as percentage of injected dose per gram of tissue (% ID/g) or per organ (% ID).

Comparisons between groups at different time points were analyzed using Student's *t* test, and $p<0.05$ was considered statistically significant.

It was shown that after intramuscular administration the total amounts of ^{103}Pd-HSA, 5-10 μm and ^{103}Pd-HSA, 20-40 μm at the site of injection didn't have statistically significant differences. At later terms the amount of ^{103}Pd-HSA, 5-10 μm in muscle decreased faster than ^{103}Pd-HSA, 20-40 μm. At 10 day postinjection (p.i.) the amount of ^{103}Pd-HSA, 20-40 μm in muscle was 61.6 % ID, whereas the amount of ^{103}Pd-HSA, 5-10 μm was only 24.9 % ID ($p < 0.001$). At 20 day p.i. the amounts of ^{103}Pd-HSA, 5-10 μm and ^{103}Pd-HSA, 20-40 μm at the site of injection decreased to 10.5 % and 16.3 % ID, respectively.

After intratumoral injection the total amount of ^{103}Pd-HSA, 5-10 μm and ^{103}Pd-HSA, 20-40 μm in tumor didn't have statistically significant differences almost at all terms of study and varied from 63.7-86.1 % ID and 76.8-82.9 % ID, respectively. Only at 20 day p.i. amounts of ^{103}Pd-HSA, 5-10 μm and ^{103}Pd-HSA, 20-40 μm decreased to 41.3 % and 73.5 % ID, respectively ($p < 0,01$).

Rather high uptake of ^{103}Pd-HSA, 5-10 μm and ^{103}Pd-HSA, 20-40 μm was observed in kidneys. Moreover, the uptake of ^{103}Pd-HSA, 5-10 μm was higher as compared with ^{103}Pd-HSA, 20-40 μm after both intramuscular and intratumoral administration.

In conclusion, particles size has an impact on the biodistribution of^{103}Pd-HSA after different routes of administration.

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THE BIODISTRIBUTION OF ^{213}BI-METALLOTHIONEIN AND ^{213}BI-IgG IN INTACT MICE

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Radiopharmaceuticals labeled with alpha-emitting radionuclides have a great potential in various cancer therapy. Alpha particles have high linear energy transfer, short penetration depth and cause irreparable double strand DNA breaks [1]. Unlike beta emitters, α-particles can damage both normal and hypoxic tumor cells [1]. The α-emitting radionuclide ^{213}Bi ($T_{1/2}$ = 45.6 min, E_α = 8.4 MeV, γ = 440 keV) appears to be suitable for targeted alpha therapy. An important advantage of ^{213}Bi is it production from ^{225}Ac/^{213}Bi generator on site.

Specifically targeted molecules, which are responsible for the selective interaction with the target, are necessary to achieve high concentration of radionuclide in tumor. It can be obtained by using of antibodies, or immunoglobulins, binding with high affinity to antigens expressed on tumor cells. Radiolabelling of antibodies mustn't lead to reduction of their immunospecific properties. For the avoidance of this drawback, we offer to radiolabel antibodies by binding them with metallothionein, which can serve as chelator for radionuclides.

The aim of the study was to investigate the biodistribution of ^{213}Bi-metallothionein (^{213}Bi-MT) and ^{213}Bi-IgG in intact mice and compare it with biological behavior of $^{213}BiCl_5$.

Metallothionein was derived from rat liver. Rats were previously injected with $KdCl_2$. Extracted liver was washed with saline and homogenized in 0.1 M tris-HCl buffer solution (pH 7.4). Obtained mixture was centrifuged at 1000 g for 20 min at 4 °C. Subsequent purification of

metallothionein was carried out by ion-exchange chromatography in column with DEAE-sepharose.

Antibodies to thyroglobulin were used as immunoglobulin model. They were got from rabbits, which were sensitized with 3 intradermal injections of thyroglobulin plus Freund's adjuvant once a week.

All animal studies were performed in intact outbred mice. Mice were divided into 3 equal groups (n = 12 for each group). Mice were injected intravenously with 0.185 MBq of ^{213}Bi-MT, ^{213}Bi-IgG or $^{213}BiCl_5$ in a volume of 0.1 ml. At 5 min, 1 and 3 h postinjection (p.i.) animals were sacrificed, organs and tissues were collected, and the radioactivity was measured using automatic gamma counter. The values were expressed as percentage of injected dose per gram of tissue (% ID/g).

The results indicated that in the most organs the biodistribution of ^{213}Bi-MT and ^{213}Bi-IgG differed from $^{213}BiCl_5$. High uptake of ^{213}Bi-MT was observed only in kidneys (up to 132.0 ± 5.5 % ID/g) and thyroid (up to 112.0 ± 9.2 % ID/g), whereas $^{213}BiCl_5$ accumulated largely in kidneys (20.9-141.6 % ID/g), thyroid (48.8-67.2 % ID/g), blood (3.98-12.5 % ID/g), lungs (6.13-13.2 % ID/g), liver (3.19-15.3 %/g) and spleen (3.08-10.4 % ID/g). ^{213}Bi-IgG was characterized by high uptake in thyroid (up to 35.2 ± 8.1 % ID/g) and kidneys (up to 79.2 ± 4.5 % ID/g). Liver uptake of ^{213}Bi-IgG varied from 4.7 to 6.6 % ID/g, that was lower than $^{213}BiCl_5$.

In conclusion, the opportunity of metallothionein usage as chelator for bismuth-213 was shown. It was found that the biodistribution of ^{213}Bi-metallothionein and ^{213}Bi-IgG differed from $^{213}BiCl_5$. But further investigations are necessary to improve ^{213}Bi-metallothionein and ^{213}Bi-IgG stability and decrease their uptake in kidneys and thyroid gland.

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IMMUNOTHERAPY: AUTOIMMUNE DISEASES, ENVENOMATION, INFLAMMATION AND CANCER

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We are conducting research on the acetylcholine nicotinic receptors (nAChR) [1] and in the frames of the present symposium will mainly concentrate on the immunotherapy approaches to treat diseases associated with malfunctioning of these nAChRs or to benefit from their activation /inhibition in such processes as inflammation, pain perception and other. Muscle nAChRs play an important role in muscle contraction, while at myasthenia gravis in most cases the reason are the autoantibodies against the nAChR α-subunit, and the immunotherapy involves periodical plasma exchange and removal of such antibodies. The word "envenomation" is present in the title because protein neurotoxins (including three-finger α-neurotoxins) from snake venoms are classical tools in the research on the nAChRs. Snake bites in Asia, Africa and South America are a serious problem, lead to numerous deaths, and preparing the appropriate antisera is in fact the only way to help by immunotherapy. The best results are achieved when in immunization of horses are utilized mixtures of venoms of different snake species or, even better, mixtures of toxins isolated from various snake venoms.

Peptides and proteins from snake venoms and from other animal sources may be considered as potential drugs, including those for immunotherapy. We have demonstrated that some α-conotoxins from the Conus marine snails and α-cobratoxin from the cobra venom inhibit the proliferation of the Erlich sarcoma cells [2].

Concerning involvement of nAChRs as targets in immunotherapy, it should be noted that α7 nAChR in macrophages plays an important role in regulation of the immune response via vagus nerve: it was shown earlier

that activation of this receptor subtype decreases the expression of TNF and thus inhibits the inflammation. We have for the first time demonstrated that α7 nAChR activation affects the expression of a number of membrane proteins on macrophages which is reflected in the inhibition of inflammation processes [3].

Regulation of the cytokine expression is of utmost importance with SARS-CoV-2 which is often is accompanied by the cytokine storm. There were hypotheses about a possibility to diminish this storm by acting on nAChRs with nicotine or other agonists, which did not yet receive a confirmation. Another important component of snake venoms is phospholipases A2 (PLA2) and for one of them we earlier found anticancer activity [4] and recently demonstrated the perspectives of these enzymes against SARS-CoV-2 [5]. Since data in literature showed that some phospholipases A2 inhibit the growth of Ebola and some other viruses, we tested a series of PLA2 from the viper venoms against SARS-CoV-2 and found that some of them in the enzymatically active form destroy the virus lipid bilayer, interact both with the ligand-binding domain of the virus S-glycoprotein and with the ACE2 - its target on the host cells [5].

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NANOPARTICLES FOR PHOTO-HYPERTHERMIA APPLICATIONS

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Nanoparticles (NPs) of semiconductor and plasmonic materials exhibit interesting physical properties, which can be used in biomedical applications. Silicon (Si) NPs (Si-NPs) are especially promising because they are biocompatible, biodegradable and can be easily prepared by chemical and laser-assisted methods [1,2]. Si-NPs in aqueous media act as an efficient absorber of light in the visible and near-infrared spectral regions and it can be used for photohyperthermia [4]. Alumina-silicate halloysite nanotubes with immobilized plasmonic gold NPs are found to sensitize and to localize the photohyperthermia under continuous wave and nanosecond pulsed laser excitation with a photon energy close to the plasmonic resonance [4]. These physical properties of semiconductor and plasmonic NPs are promising for mild therapy of cancer.

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ADVANCED BINARY HADRON THERAPY TECHNOLOGIES

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The program of development and implementation of new diagnostic and therapy technologies based on the Proton Therapy Complex (PTC) "Prometheus" is presented. The tasks will be implemented with the close integration of the LPI, MEPhI, Center of Radiology, Kurchatov Institute, as well as their Russian and foreign partners.

Modernization of Russian-made proton synchrotron complexes of the Prometheus system is envisaged in order to develop and implement new technologies based on them and improve existing technologies for proton and ion therapy and diagnostics. Prometheus is a unique PTC. It is a compact (outer diameter - 5 m, weight – 15 tons) synchrotron for protons with low energy consumption (up to 100 kW), which allows one to place such PTCs directly in medical centers.

It is supposed to develop proton radiography and tomography technologies using the maximum proton energy. Technologies of combined action of various types of radiation (protons-neutrons, protons-carbon ions, multi-ion therapy); targeted proton therapy technologies using promising nanoparticles and systems based on them as therapy sensitizers and active agents for diagnostics.

The latter direction involves a significant expansion of the field of modern nuclear medicine through integration with nanomedicine, which uses nanoparticles for the diagnosis and therapy of cancer, using their unique properties. The introduction of non-radioactive materials that can be activated from the outside using various external sources of nuclear particles to produce radioactivity in situ is one of the new directions of activation of nano-drugs at the site of a cancerous tumor, which can be considered as in situ production of radiopharmaceuticals.

Modernization of Prometheus PTC based on the developed nuclear physics technologies, their production for Russian nuclear medicine centers opens the way for solving the issue of development and introduction of new effective technologies for proton and ion diagnostics and therapy.

PHARMACOKINETIC OF MAGNETIC NANOPARTICLES IN THE ORGANISM

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Safe application of nanoparticles in medicine requires full understanding of their pharmacokinetics including blood circulation time, biodistribution and long-term fate of nanoparticle residue. In this study we describe a magnetic spectral approach for non-invasive and quantitative monitoring of magnetic particles in the organism. We investigated influence of various physicochemical properties of particles on the blood circulation time and degradation rate in the liver and spleen [1,2].

Namely, we studied the following 9 factors: particle size, zeta-potential, coating, injection dose, repetitive administration, induction of anesthesia, mice strain, absence/presence of tumors, tumor size. We observed a slowdown in magnetic particle biotransformation with an increase of the injected dose and faster degradation of the particles of a small hydrodynamic size. Also, tumor growth led to a decrease in a particle residence time in the blood.

We believe that deeper understanding of the underlying mechanisms may considerably facilitate the rational design of non-stealth nanomaterials with advanced surface functionality and superior pharmacokinetics for the next generation theranostics.

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POSTER REPORTS

PHOTODYNAMIC THERAPY OF PRECANCEROUS DISEASES OF THE ORAL CAVITY AND LARYNX

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Aim. The relevant problems of modern oncology are timely diagnosis and effective treatment of precancerous conditions of the oral cavity and larynx. Also early diagnosis of precancerous lesions and oral cancer is complex. It is often associated with an asymptomatic disease course, and differentiating pathological tissue from relatively healthy tissue is often difficult [1]. The lack of timely diagnosis and treatment of precancerous conditions contributes to their further transformation into a malignant tumor. Mortality from oral cancer in most countries is high, and the 5-year relative survival rate is about 50% [2].

The study aimed to develop a method for sublingual administration of 5-ALA to patients and to evaluate its effectiveness in fluorescent diagnosis and photodynamic therapy of neoplasms of the oral cavity and larynx.

Material and methods. Sixteen patients aged 56 ± 12 with precancerous diseases of the oral cavity and larynx were included in the study. The patients took a 5-ALA sugar syrup at a concentration of 20 mg/kg sublingually. The boundaries of the neoplasms were established by the video-fluorescence diagnostics and clarified using spectral-fluorescent diagnosis before and after photodynamic therapy. A two-channel video system was used for video-fluorescence diagnostics, fiber spectrometer LESA-01-BIOSPEK and helium-neon laser (λ = 632.8 nm, Pmax = 15

mW) for spectral-fluorescent diagnosis, semiconductor laser (λ = 635 nm, P_{max} = 1.5 W) for PDT (E_s = 100–200 J/sm^2).

Results. According to the results of video fluorescence and spectral fluorescence diagnostics before PDT, protoporphyrin IX with sublingual administration of 5-ALA to patients accumulated several times more in pathologically altered tissues than in normal ones and burned out more than 60% after PDT.

Glucose contained in the sublingual dose supports active transport of 5-ALA into the cells. Positive dynamics of treatment were noted in patients with papillomatosis of the larynx and oral cavity. Leukoplakia and oral dysplasia were not detected after PDT. Repeated PDT was required for two patients with leukoplakia. As a result, of PDT, leukoplakia was eliminated. The results of the study indicate that PDT is effective for the treatment of premalignant lesions of the oral cavity and larynx.

Conclusion. The study demonstrated the possibility and effectiveness of laser-induced PD and PDT with sublingual administration of 5-ALA to patients with premalignant lesions of the oral cavity and larynx. It can eliminate the threat of the transformation of these diseases into malignant tumors and save the patient from surgical treatment.

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CYTOGENETIC EFFECTS OF COBALT AND IEAD IONS IN THE ROOT MERISTEM OF BARLEY

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Various types of modern production are powerful sources of pollution of the biosphere with heavy metals, which negatively affect living organisms and the degree of this influence must be assessed, especially when it comes to food quality issues, for example, in the production of agricultural products [1].

The cytogenetic effects of lead and cobalt ions on barley seedlings of the spring variety Josephine were studied in the laboratory experiments [2]. The possibility of reducing the negative effects of lead in the presence of cobalt ions in the seed germination solution was evaluated. When evaluating the combined action of heavy metal ions, the seed soaking solution contained Pb^{2+} and Co^{2+} in concentrations corresponding to the same MPC values. The experiment was repeated four times. The criteria for the manifestation of cytogenetic were the following indicators: the frequency of aberrant cells and the mitotic index - the percentage of dividing cells from the total number of analyzed cells. The results obtained were compared with the results in the control, where the seeds were germinated in distilled water.

The content of lead ions in the solution for germinating barley seeds led to a significant ($p<0,05$) decrease in the germination energy, a decrease in the mitotic index and an increase in the frequency of aberrant cells in comparison with the control values already at a metal concentration of 0,1 MPC for drinking water. The presence of cobalt ions in the seed germination solution also led to a change in the value of these parameters [3]. However, significant differences with the control were at an ion concentration equal to 1 MPC. A decrease in the negative effects of lead was revealed when it is present together in a solution for germination with cobalt ions. In this case, the higher the concentration of

heavy metal ions was, the stronger the compensating effect of Co^{2+} was. It was found that in the presence of lead ions, the quantitative yield of aberrant cells per concentration unit is 2,14 times higher compared to the combined presence of two metal ions. Antagonism coefficients, calculated according to the index of aberrant cells in the separate and joint presence of metals at concentrations equal to 0,1, 1 and 10 MPC, were equal to 0,19; 0,35 and 0,41 (fig.1). It was suggested that it is possible to use cobalt-containing agrochemicals (plant growth regulators, dietary supplements, complex fertilizers) as agents that reduce the toxic effect of heavy metals, lead in particular.

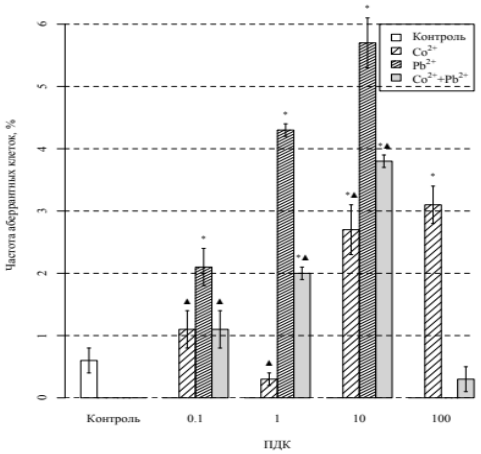

Fig. 1. The effect of cobalt and lead ions in various concentrations on the frequency of chromosomal aberrations and lags in the cells of the root meristem of barley seedlings of the Josephine variety

* - differences with control are significant at p <0.05; 1 MPC (for drinking water) for Co2 + is 0.01 g / l, for Pb2 + - 0.005 g / l

▲ - differences with the Pb2 + variant are significant at p <0.05

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ANTIBIOTIC THERAPY IN INFECTED PANCREATIC NECROSIS, FEATURES OF THE COURSE OF METABOLIC CHANGES IN THE ORGANISM

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In modern surgery, the systemic inflammatory response syndrome is of great importance. Leading mechanism of the occurrence of this syndrome is the uncontrolled spread of proinflammatory cytokines in the blood.

Our task was to investigate the associative role of other factors in the path-ogenesis of systemic inflammatory syndrome, in particular the process of lipid peroxidation, phospholipase systems, endogenous intoxication, disorders in the hemostasis system, which are given scattered.

The experiments were conducted on 56 adult dogs. Acute severe pancreatitis was created by the method of V. M. Buyanov et al. (1989).

In the control periods (1st, 2nd, 3rd, 4th and 5th days), a relaparotomy was performed, in which the severity of inflammation of the pancreas was as-sessed, blood was taken.

The work uses research methods to assess the peroxidation of membrane lipids, endogenous intoxication, phospholipase activity, and the state of the he-mostasis system.

The digital data were processed by the method of variational statistics us-ing the *Student's* criterion t and $\chi 2$, the correlation dependence was the criterion *r*.

In experimental biliary total pancreatic necrosis, there is a disorder of homeostasis, manifested by an increase in endogenous intoxication, intensifica-tion of lipoperoxidation processes, phospholipase activation, and disorders in the hemostasis system. When monitoring these patho-

logical processes, it turned out that they progress in the blood plasma up to 3 days after the simulation, and there was no significant increase in the intensity of these processes in subsequent periods. It is also interesting that the addition of such a component, as infection, to the factor of occurrence of biliary total pancreatic necrosis did not lead to the progression of the systemic inflammatory response syndrome and was not ac-companied by a significant change in the studied processes.

The use of antibiotic therapy in experimental animals with biliary-purulent total pancreatic necrosis does not prevent the development of a systemic inflam-matory response. There is only a significant decrease in the severity of endoge-nous intoxication. This condition is explained by the fact that such a pharmaco-logical effect cannot, timely, adequately and fully function, first of all, the patho-logical changes developing in the tissue structures of the main vital internal or-gans. Such pathologically abnormal processes include, first of all, the normal course of free radical processes of lipid peroxidation, hypoxia and accumulation of tissue factors affecting the hemostasis system. They cause the development and progression of enteral, hepato-renal, cardiac and respiratory insufficiency.

Consequently, experimental studies indicate the need for the complex treatment of biliary or biliary-infected severe pancreatitis of such a component that would therapeutically affect the above processes.

DEBYE MODEL AND THE CIRCUIT MODEL: SOME STRATEGIES FOR IMPEDANCE DATA PROCESSING

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Equations of Debye Model have been considered for describing of ferrofluid dielectric properties. Also, it is possible to use impedance equations of the circuit model for the same purpose. Problems with solving the equations with a high degree do not allow to get accurate formulas for resonance frequencies, however, it is possible to use approximations, these approximate solutions allow to claim that poles can be used data processing with both models discussed above. For example, for the understanding of conditions for the parameters of models considered poles can be applied. The theoretical work is considered within the framework of preparations for the next experiments.

In the case, if dc conductivity σ_D, high frequency and static dielectric constants ε_∞ and ε_s respectively, and relaxation time τ_D are real numbers, the effective dielectric constant from Debye model [1] in the approximation of one relaxation time is (1):

$$\varepsilon(\omega) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + i\omega\tau_D} - i\frac{\sigma_D}{\omega}. \quad (1)$$

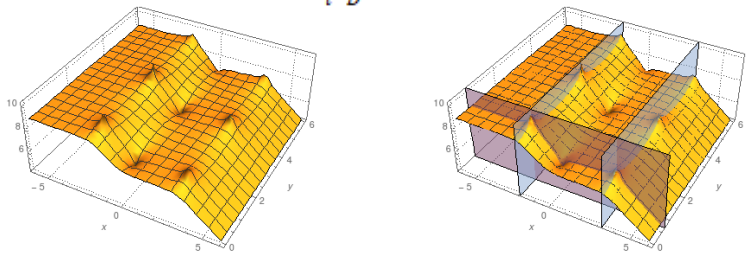
Complex impedance can be presented like $Z(\omega) = 1/(i\omega C(\omega))$ (ω is the cyclic frequency, f is the frequency), here $C(\omega)=\varepsilon(\omega)(S/d)$. If $R(\omega)$ is a real part of the impedance and $X(\omega)$ is an imaginary part of impedance, then the effective dielectric constant can be presented as (2):

$$\varepsilon(\omega) = \frac{d}{i\omega S\big(R(\omega) + iX(\omega)\big)}. \quad (2)$$

Formulas of both relaxation time τ_D, and dc conduction σ_D were obtained on the basis of impedance poles, here ω_h is the cyclic frequency of the local minimum of the imaginary part of the impedance at high frequency region, ω_l is the same at low frequency region (3, 4):

$$\tau_D \approx \left| \frac{\varepsilon_\infty \omega_l + \varepsilon_\infty \omega_h - \sqrt{-4\varepsilon_\infty \varepsilon_s \omega_l \omega_h + \varepsilon_\infty^2 (\omega_h + \omega_l)^2}}{2\varepsilon_\infty \omega_h \omega_l} \right|. \quad (3)$$

$$\sigma_D \approx \left| \frac{\omega_l (\varepsilon_\infty \tau_D \omega_l - \varepsilon_s)}{\omega_l \tau_D - 1} \right|. \quad (4)$$



(a) *(b)*

Fig.1. 3D plot of the decimal logarithm of the impedance absolute value for Debye model without (a) and with (b) planes showed some poles

Fig. 1 presents 3D plots for Debye model ($log_{10}(f) = x + i\,y$). Also, the presented approximation for the circuit model could be mathematically considered if $|\omega| < |\omega_b|$and $|\omega| < |\omega_s|$, here ω_b is ω_h and ω_s *is* ω_l (they described the base and the surface influence resp.).

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APPLICATION OF PHENOMENON OF ANOMALOUSLY SLOW RELAXATION OF A NON-WETTING LIQUID DISPERSED IN THE PORE SPACE FOR DRUG DELIVERY

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The aim of reducing the toxic effects of drugs on the human body has existed for decades [1]. The ideal solution to this problem could be targeted delivery of drugs only to the focus of the disease without spreading throughout the body. One of the promising materials for targeted drug delivery is a nanoporous material containing an active drug [2, 3]. In recent years, a unique phenomenon has been discovered in nanoporous material - non-wetting liquid systems, namely, anomalously slow relaxation of a non-wetting liquid dispersed in the pore space [4]. This phenomenon, depending on the components of the system and on external conditions, can be used for the delivery of drugs with a prolonged effect.

The results of the study of the system nanoporous material Fluka 100 C18 (#60756-50G) manufactured by Sigma Aldrich - a non-wetting liquid 24 μM doxorubicin solution in saline are presented in the paper. The study of the phenomenon of anomalously slow relaxation in the temperature range of 5 - 40 ^{0}C at times from 1 to 10^4 seconds was carried out according to the methodology described in the paper [4]. The study of the influence of the pH of the surrounded medium on the extraction of doxorubicin solution into buffer solutions with pH =5.0 and pH = 7.4

was studied at a temperature of 40 ^{0}C using the spectrophotometer HACH LANGE DR 5000 at times from 1 to 6000 seconds.

It is shown that the temperature has a critically effect on the part of the liquid that not outflow. The temperature increase from 5 to 40 ^{0}C reduces the part of non-outflow liquid from 98 to 18%. Also for all temperatures was observed the phenomenon of anomalously slow relaxation. The study of the influence of the pH of the surrounded medium is shown a predominant release of doxorubicin solution into a buffer solution with pH = 5.0.

According to the results of the studies, it can be concluded that the studied system has the property of predominant outflow of a doxorubicin solution from the nanoporous material into the surrounded medium with increased acidity (corresponding to cancer tissues) and the prolonged effect.

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PLASMONIC SILVER NANOPARTICLES AS AN AGENT FOR CANCER TUMORS PHOTOTHERMAL THERAPY

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Nowadays, the development of targeted cancer therapy is on the cutting edge in tackling global biomedical problems in oncotherapy and oncodiagnostics. Metal nanoparticles (NPs) produced by the "green" synthesis method, possessing the property of localized surface plasmon resonance, are considered as the one of the most promising agents for photothermal cancer therapy [1-8].

In the course of this study, for the first time, plasmonic silver NPs were obtained by the "green" synthesis method with aqueous extracts of intact lavender (*Lavandula angustifolia* Mill.) green parts [9]. As-obtained NPs were characterized by spectrophotometry, dynamic light scattering, and scanning electron microscopy. Silver NPs were found to be colloidally stable in phosphate-saline solution with optimal for nanotheranostics size of 35 nm. NPs were modified with a scaffold polypeptide highly selectively recognized the HER2 tumor marker both *in vitro* and *in vivo*. The cytotoxic, hyperthermic properties, as well as the process of internalization of NPs, were studied on cell lines of various tissue origins. We showed that the obtained NPs possess cytotoxic properties against HER2-positive cells with non-significant toxicity for HER2-egative cells. The synthesized silver NPs can be used for local hyperthermia: upon the blue light irradiation an increase in the temperature of the solution with NPs by 10 °C was observed. The photothermally-induced death of HER2-overexpressed cancer cells was shown *in vitro*. For the first time, the anticancer efficacy of the obtained NPs was investigated *in vivo* using xenograft tumors. The complete remission was shown when treating BALB/c Nu/Nu mice with intratumoral injec-

tions of NPs modified with affibody in combination with external irradiation of the tumor with blue light.

The research was supported in part by the Russian Science Foundation grant, project No. 17-74-20146 (nanoparticle synthesis, *in vivo* studies) and the Russian Foundation for Basic Research, project No. 19-29-04012 (*in vitro* studies).

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EFFECTS OF MPS BLOCKADE WITH LIPOSOMES ON PHARMACOKINETICS OF MAGNETIC NANOPARTICLES

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Magnetic nanoparticles are a powerful theranostic agent most frequently delivered *in vivo* by a passive accumulation in target tissues. However, the considerable disadvantage of passive-targeted nanoparticles is their predominant accumulation in macrophage-rich organs, such as liver and spleen. One of the strategies to change the biodistribution and prolong the blood-circulation lifetime of nanoparticles is to block the mononuclear phagocyte system (MPS) [1].

Unfunctionalized empty liposomes have the similar tendency to passively accumulate in the liver and spleen, thus saturating cells of the MPS. Therefore, liposomes are considered a promising tool for induction of MPS blockade for boosting nanomedicine efficiency [2].

In this study, we demonstrated that the kinetics of blood-circulation of 100-nm magnetic particles may be prolonged 3-fold by a preinjection of liposomes (fig. 1a). Also, it decreases the liver uptake of particles and enhances accumulation in the spleen and lungs (fig. 1b).

The results of this study could be used to achieve a more appropriate pharmacokinetic profile of passively targeted magnetic nanoparticles via inducing MPS blockade.

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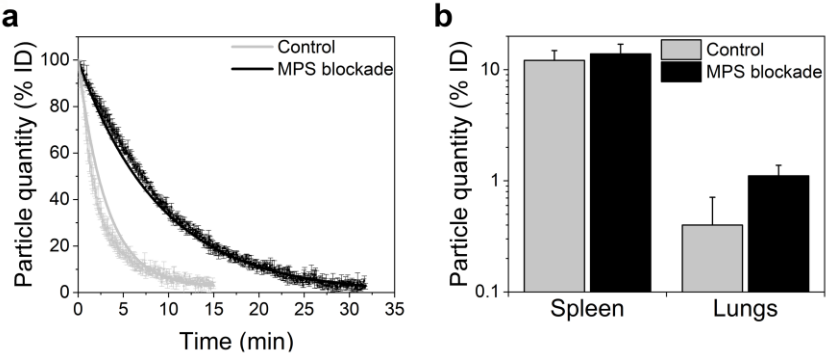

Fig. 1. Blood circulation kinetics (a) and biodistribution (b) of magnetic particles with and without administration of the MPS-blocking liposomes

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POLYMORPHISM OF OBESITY GENES IN STUDENTS OF DIFFERENT ETHNICITIES

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It was found that body weight and propensity to obesity are caused not only by environmental influences (level of physical activity, dietary habits, etc.), but also by genetic factors that affect the variation of body mass index (BMI) within 65-80% [1].

To identify a possible polymorphism of ADRB2 and ADRB3 genes associated with fat mass, 64 students of IATE MEPhI of different ethnicity were examined. The students were divided into four groups by country affiliation: Group 1 – European students – 25 people, group 2 – African students – 20 people, group 3 – Vietnamese students – 14 people, group 4 – students of different nationalities – 5 people.

Before the analysis, medical and genetic information was collected from all the examined persons, anthropometric measurements were carried out to calculate the BMI. To clarify the value of BMI in all subjects, the type of fat distribution in the human body was determined.

According to the results of the survey, we assumed a genetic predisposition to obesity in 39% of students. For all the examined individuals, we conducted a real-time PCR analysis to determine the genotype by the ADRB2, ADRB3 genes responsible for the genetic predisposition to obesity.

According to the results of PCR analysis, it was possible to determine: a normal variant of gene polymorphism (there is no mutation), a mutation in a heterozygous form (in one of the paired genes), a mutation in a homozygous form (in both paired genes). The results are presented in Tables 1-2.

Table 1. Polymorphism of the ADRB2 gene

	Europeans	Africans	Vietnamese	Other ethnic groups
Homozygote for allele 1 (no mutation)	8%	30%	57,2%	20%
Heterozygote	44%	60%	35,7%	80%
Homozygote for allele 2	48%	10%	7,1%	0%

Table 2. Polymorphism of the ADRB3 gene

	Europeans	Africans	Vietnamese	Other ethnic groups
Homozygote for allele 1 (no mutation)	92%	65%	78,6%	60%
Heterozygote	8%	35%	21,4%	40%
Homozygote for allele 2	0%	0%	0%	0%

The results of the analysis of genes for polymorphism confirmed the predisposition to obesity in 96% of individuals who, as we assumed according to the questionnaire, have a genetic predisposition.

It is of interest to further study the association of candidate genes for the development of obesity and the cluster of metabolic parameters in other ethnic groups of Russia.

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VALIDATION THE SOFTWARE APPLICATION FOR QUANTIFICATION OF GADOLINIUM CONTRAST AGENTS IN LABORATORY MICE IN VIVO

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In 1959 the "concept of three R's" (reduction, refinement and replacement) was introduced by William Russell as the basic ethical principle of laboratory animal welfare. So non-invasive methods of study in vivo are preferable for researching with laboratory animals. Thus, a special software application was developed to ease the process of following this concept for researchers. It allows obtaining a concentration map of Gd-based contrast agent (CA) for laboratory mice with subcutaneous tumor in vivo. [1-2] This study focused on validation of this application, that is, comparing concentration analysis results of such calculations with the expected distribution.

At the first step, the relaxivity of the CA (Gadovist) was calculated to create a map of the concentration of Gd-based CA. For this, MR phantoms with Gadovist were used. Its solvent was an artificially created blood serum that simulates the blood of a mouse. At the second step, images were obtained on MRI scanner for laboratory mice with subcutaneous tumor before and after the injection of CA. These images were processed by the app to calculate T1 relaxation time maps before and after CA injection and concentration maps. [3] After analyzing the intensity of the signals on the MR images, assumptions were made about the values of T1 relaxation and Gd concentrations that should be observed on the maps. The results generally obtained confirmed the assumptions. However, Gd-based contrast agents affect both the longitudinal and transverse relaxation components. One or another process dominates depending on the Gd concentration. A wide range of gadolin-

ium concentrations can be observed in its biodistribution study in a mouse. Therefore, T2-shortening effects can predominate in some areas. And it can lead to an incorrect estimate of the Gd concentration. To solve this problem, a way to improve the app was proposed. It includes obtaining additional MR images of laboratory mice with and without CA. Then, by analyzing the image data, one can create T2 relaxation maps [3] and additionally calculate the Gd concentration.

Thus, this software application for estimation of Gd concentration in vivo shows reliable results only for the regions where CA actually causes a reduction in longitudinal relaxation times. However, there are areas in which the largest contribution to the signal intensity comes from T2 relaxation processes. And to account for them, an application upgrade is required.

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MATERIALS AND TECHNIQUE FOR INTRAOPERATIVE VISUALIZATION OF PARATHYROID GLANDS DURING THYROIDECTOMY

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Identification and preservation of parathyroid glands (PGs) during the surgery are crucial for preventing postoperative hypocalcemia following thyroidectomy. Despite of that the surgical technique is constantly evolving, the postoperative hypocalcemia remains to be one of the well-recognized complications of thyroidectomy (30%) [1]. Autofluorescence (AF) of PGs is a recent technique that aims to help with the intraoperative identification of parathyroid glands during thyroidectomy [2]. In addition to the AF technique, the accuracy of the PGs identification can be improved by using a multimodality approach to better differentiate tissues [3]. Moreover, besides the AF signal in the infrared spectral range, it should be a specific heat release from PGs after photoexcitation because of the photoinduced heating of biotissue.

Our work is aimed to develop a technique for intraoperative visualization of normal PGs during total thyroidectomy based on the combined thermographic - AF imaging.

High-resolution CCD spectrometers were used for the AF detection. Semiconductor lasers with wavelength of 650 and 660 nm and intensity up to 180 mW were used to excite the fluorescence of PGs. The thermography was performed by using a Flir ONE Pro LT (USB-C) IR imager. To suppress the scattered laser radiation, we used a self-made filter, which was prepared from porous silicon (PS) layers obtained by using the standard method of electrochemical etching of crystalline silicon wafers in a hydrofluoric acid solution [4]. The filter was composed by several PS layers forming a 1D photonic crystal. To realize the electro-

chemical etching, a current source was programmed by using Python 3.9 software. An analysis of the interference maxima and minima in the transmission spectrum of PS film was carried out to determine the effective refractive index, which was used to define the electrochemical etching time. The optical properties of PS filters, such as the attenuation coefficient (approximately ~ 10^4), effective refractive index (1.8- 2.5), thickness (8 – 15 μm) were determined. The PS filter narrows the bandwidth in the near infrared range. At the same time, it has been proven that we could detect the photoheating and cooling of model biotissue pieces, i.e. moles. Temperature fluctuations were about 1.5 ºC. This fact allows us to assume the same approach for the thermography of PGs during the intraoperative identification.

Then, our results and analysis of the literature indicate that among actual methods of the parathyroid gland identification the thermography can be efficiently combined with fluorescent diagnostics. The simultaneous detection of the photoinduced heating of biotissue and its autofluorescence allows us to improve the special resolution for the PG identification. The optical signal filtering is improved by using 1D photonic crystals based on porous silicon. Further development of the method requires optimization of the exciting laser parameters as wavelength and intensity.

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CEREBRAL INTRACELLULAR ACIDIFICATION IN CHILDREN WITH CONCUSSION. 1H MRS STUDY

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Introduction

Concussion is a mild form of traumatic brain injury (mTBI) with short-term loss of consciousness. On the one hand, it does not lead to structural changes visible by standard MRI or CT. However, on the other hand, it may have some long-term consequences, for example reduced attention, memory and sleep disturbances, increased irritability and fatigue, frequent dizziness and headaches [1]. Therefore, there is a necessity to search for biochemical changes in brain by alternative method – Magnetic Resonance Spectroscopy (MRS). The main goal of the current study was to determine changes in the values of pH in mTBI using MRS methods.

Materials and methods

The study involved two groups: 16 patients with mTBI and 17 healthy controls. Mean age was 15 ± 3 years. The study of patients was carried out in the acute period - up to three days from the day of injury. The MRI examination (Philips Achieva dStream 3.0T) included standard protocols for TBI, in which no changes were found. The MRS protocol included a PRESS sequence: TR = 2 s, TE = 80 ms. The voxel (50 x 25 x 25 mm) was located in the posterior cingulate cortex. The values of the central frequency of the signal in the region of 7 ppm were determined and the pH values were calculated using the expression from[2].

Results and discussion

The main result of the current work was the detection of a change in the values of pH. The difference in the chemical shifts of the averaged signals was approximately 0.01 ppm (figure 1). Which corresponds to a 1.2% decrease in the pH value in mTBI. This effect can be explained by a violation of blood microcirculation in the vessels, as a result of which the anaerobic stage of glycolysis is activated and lactate accumulates in this area.

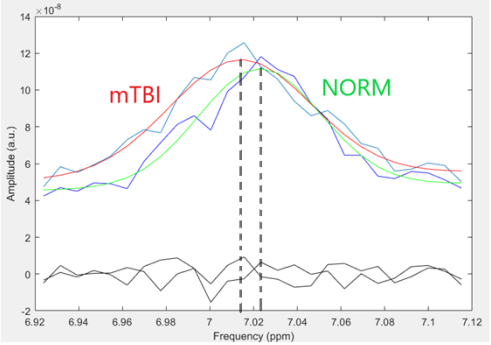

Fig.1. Overview of the signals averaged over groups (NORM and mTBI) at 7 ppm and approximation of the signals

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ENDOSCOPIC INJECTION OF PLATELET-RICH AUTOPLASMA IN TREATMENT OF REFRACTIVE GASTRODUODENAL ULCERS, COMPLICATED WITH BLEEDING

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Relevance. Endoscopic remains the main instrumental method for achieving hemostasis in ulcerative gastroduodenal bleeding (UGDB). The problem of recurrences of UHDC determines in this category of patients high rates of overall mortality in general and requires further study. [1,2] The most problematic is the group of age patients with a severe comorbid background, which are characterized by refractory gastric and duodenal ulcers [3], and the occurrence of UGDB aggravates the already existing systemic and local disorders. For such patients, no effective method has been proposed for influencing the source of UHD in order to stop bleeding and accelerate repair, since any methods of endohemostasis either aggravate destructive processes in the area of the ulcer, or are not effective enough.

Platelet-rich plasma (PRP) is currently actively used in various branches of medicine, reliably leading to an acceleration of the epithelialization process. [4] However, we did not find any reports on the use of PRP injections to accelerate the healing of ulcer defect and prevent recurrence of UGDB in the available literature.

Purpose of the study: To study the effect of endoscopic submucosal PRP injections on the healing of refractory gastroduodenal ulcers and the prevention of delayed recurrence of bleeding in comorbid patients.

Materials and methods: For the clinical study, 58 patients with bleeding were selected, in whom no signs of the onset of epithelialization of the ulcer defect were noted within 10 days (stage A1-A2 according to the Sakita-Miwa classification). All patients underwent standard conservative therapy after endoscopic arrest of bleeding. Among the patients, men predominated - 41 patients (70.7%), women were 17 (29.3%). The age of the patients varied from 48 to 75 years, the average age was 68 ± 7 years. The comorbidity index for CIRS-G is 18 ± 4 points, the severity of the APACHE II condition is 20-24 points. PRP was obtained using the PlasmoliftingTM technology. [5]

Group I included 30 (51.7%) patients in whom, in order to accelerate the process of epithelialization of the ulcer and prevent late recurrence of bleeding, endoscopic injections of OTFA were performed into the submucosal layer along the perimeter of the ulcer at 4-5 points with subsequent application to the surface of the ulcer. defect 1-5 ml of Hemocompact glue. The second group included 28 (48.3%) patients in whom endoscopic PRP injections were not performed. Patients of both groups underwent complex standard conservative therapy.

Every 2 days, a program endoscopy was performed until the appearance of positive dynamics - the beginning of healing of the ulcer (stage H Sakita-Miwa).

Results and discussion: As a result of treatment in the main group of patients, the appearance of granulations in the ulcer area was noted on the 5 ± 1 day of treatment, while in all patients from the main group there were no recurrences of UGDB. In patients from the control group, the onset of epithelialization of gastric ulcers and duodenal ulcers was noted on day 9 ± 1 ($p < 0.05$), while recurrent bleeding was noted in 2 patients on days 3 and 5 of treatment.

Conclusions: Endoscopic injections of PRP into the submucosal layer along the perimeter of gastroduodenal ulcers lead to an acceleration of epithelialization of ulcers by 1.5-2 times and prevent relapse of delayed bleeding in comorbid patients with long-term non-healing gastroduodenal ulcers.

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FEATURES OF THE CHRONIC WOUND PROCESS AGAINST THE BACKGROUND OF POCTCOVID SYNDROME

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Summary. Treatment of chronic wounds is a global problem for patients with severe comorbid pathology. The clinical features of the course of chronic wounds against the background of postcovid syndrome, the treatment of such patients in the context of the SARS-CoV19 pandemic have not been studied and are of great interest. In this article, we present our clinical observations on the example of 16 patients with chronic wounds of various localization in the postcovid syndrome.

Purpose of the study. To investigate the features of the course of a chronic wound process against the background of postcovid disorders.

Materials and methods. The results of outpatient treatment of 16 elderly and senile patients with long-term non-healing wounds after SARSCoV19 were analyzed. The duration of previous treatment (inpatient + outpatient) without achieving wound healing ranged from 30 days to 3 months. The terms of treatment after the transferred SARSCoV19 were 6-12 months.

Results. Comprehensive examination, according to the protocol, indicated a nonspecific chronic wound process. The following microflora was inoculated in all patients: Staphylococcus epidermidis 1x102, Escherichia coli 1x 103. Transient microflora, which had no diagnostic value, or was not inoculated at all, was inoculated in the studied biomaterial. Wound defect repair was assessed in 14 patients, 2 patients dropped out due to death

due to acute cardiovascular failure. Complete closure of the wound defect within 14 weeks was achieved only in 10 out of 14 observed patients. In 4 patients with venous trophic ulcers of the legs, the repair was not fully achieved.

Conclusion. The main distinguishing factors that characterize the chronic course of the wound process in the postcovid syndrome, according to our observations, are: 1) prolonged (5 + -1.5 weeks) course of the inflammation phase against the background of angiopathy, while at the bottom of the wound there are thrombosed non-bleeding vessels, microbial the landscape is not clinically relevant; 2) the course of the repair phase with a prevalence of coarse, fibrous granulations, depleted in vessels, an increase in the duration of the phase itself in time, despite stimulating treatment. Considering the specific pathomorphological and pathophysiological changes, the clinical examination protocol should be expanded to include the study of C-reactive protein, IgA, endothelial nitric oxide synthase assay, type 3 NOS3: 4b / a VNTR polymorphism (4a / 4b), immunohistochemical, electron microscopic, capillaroscopic research, and rheumatologists and virologists should be involved in the multidisciplinary team for the treatment of chronic wounds.

Key words: chronic wound process, postcovid syndrome, PRP-therapy.

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PRESENT METHODS OF USING HIGHLY COHERENT RADIATION IN VARIOUS FIELDS OF BIOMEDICINE

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Biomedicine is a branch of medicine that studies the human body, its structure and function in normal and pathological conditions, methods for their diagnosis, correction and treatment [1]. At present, thanks to modern advances in laser physics, many opportunities have appeared that make it possible to carry out the most complex medical research and practically apply complex techniques in the field of biomedicine. The report will consider various, most relevant technologies for the application of highly coherent radiation in various fields of biomedicine.

A promising possibility of conducting a blood test in terms of using the properties of green laser radiation in tests for determining a blood group will be considered. The importance of such a procedure lies in the fact that in the event of an urgent need for a blood transfusion, errors can lead to intravascular hemolysis, as well as to the death of the recipient [2].

Also coherent radiation is used in microdissection and pressure ejection (LMPC) technologies. They allow you to isolate a tiny area of interest - for example, a cluster of cells, a single cell, or a nucleus from a tissue sample - and isolate it for further study [3].

A promising method of infrared imaging makes it possible to classify tissues reliably, as well as automatically, and independently of the operator, which is necessary for the timely identification of tumor areas [4].

Optically pumped magnetometers (OPMS) can achieve high sensitivity for detecting brain activity (magnetoencephalography) and magnetocardiography in adult and fetal heart muscles [5].

Thus, the report shows that modern technologies using current methods of laser physics have a decisive impact on the development of biomedicine.

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FLUORESCENCE STUDY OF THE ACCUMULATION AND PHOTOBLEACHING OF 5-ALA AND HEXYL AMINOLEVULINATE - INDUCED PROTOPORPHYRIN IX IN NEOPLASM TISSUES

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Aim. 5-aminolevulinic acid (5-ALA) is a hydrophilic molecule with low penetration through intact epithelium or cell membranes [1]. Therefore, the formation of 5-ALA-induced protoporphyrin IX (PpIX) is often limited to the surface layers of tissues [2]. While its esters have better diffusing properties due to increased lipophilicity, the level of fluorescence induced by lipophilic esters is higher than with the use of 5-ALA [3]. Also, this property of esters contributes to a more rapid accumulation in cells and inclusion in biosynthesis as precursors of PpIX [4]. Previous studies indicate that hexyl aminolevulinate (HAL) causes the greatest PpIX formation [5].

This study aims to conduct a comparative analysis of 5-ALA and HAL for photodynamic diagnostics (PD) and therapy (PDT) of cervical dysplasia and vulvar leukoplakia in continuous and pulsed laser irradiation mode.

Material and methods. The study included 2 patients with cervical dysplasia and 5 patients with vulvar leukoplakia. The application method was used to deliver 5-ALA and HAL. To carry out PD in the spectral range of 615-725 nm, an LESA-01-BIOSPEC spectrum analyzer was used. For PDT, a semiconductor laser with a wavelength of 635 nm (114 J/cm^2) and a flash lamp providing radiation with an energy of 600 J/pulse (32 J/cm^2) were used.

Results. 2 hours after the application of HAL, the fluorescence intensity was almost 5 times higher than in the case of 5-ALA. In the case of cervical dysplasia and vulvar leukoplakia, the maximum value of the fluorescence index was observed with the use of HAL, which corresponded to the concentration of PpIX more than 20 mg/kg and 15 mg/kg, respectively. After PDT in a continuous mode of irradiation, intraepithelial changes were absent in patients with cervical dysplasia, whereas several patients with vulvar leukoplakia were prescribed a repeated course of PDT after pulsed light irradiation.

Conclusion. The use of HAL made it possible to achieve the highest contrast in pathologically altered tissue relative to healthy PD. Pulsed irradiation made it possible to avoid the use of anesthesia, whereas with continuous irradiation, patients experienced pain of varying degrees from a burning sensation to sharp pain in the photodynamic impact zone.

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SPECTRAL PHOTOMETRY BASED ON DIGITAL CCD-CAMERA IMAGE

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After the invention and development, charge-coupled devices (CCDs) have found wide application in technology, medicine, and scientific research [1-3]. CCD detectors are used to register radiation in various spectral ranges from far infrared to hard X-rays, including IR, visible, UV, VUV, soft X-rays. The advantage of CCD-based detectors is the ability to store and transmit digital data. The data is generated in the form of images (monochromatic, polychromatic). In this regard, CCDs are actively integrated into modern high-tech installations.

In the presented work, we propose a method for measuring the spectral sensitivity of the CCD matrix of a digital camera for the possibility of assessing the energy characteristics of the radiation recorded by the camera. This method is based on capturing an image of a radiation source and further digital processing of the image. The presented method makes it possible to estimate the values of the registered energy using only a digital image of the emitting object.

The results of measurements of the spectral sensitivity of the CCD matrix of a digital camera Canon EOS D30 in optical and near-infrared spectral range (for wavelengths of 0.532, 0.632 and 1.064 μm) are presented. The maximum sensitivity value corresponds to $4.8\ 10^{-11}$ J/(cm^2 div) for a wavelength $\lambda = 0.532$ μm, the minimum value is $4.2\ 10^{-6}$ J/(cm^2 div) for $\lambda = 1.064$ μm.

It should be noted that the characteristics of CCD matrices of a digital camera are individual, as evidenced by experiments and analysis of literature data. Thus, for correct measurements with CCDs, it is necessary to calibrate each detector used.

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HIGH-RESOLUTION METHODS FOR 3D NANOSTRUCTURE ANALYSIS AND VISUALIZATION

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Several high-resolution techniques have been used to characterize and visualize nanostructures [1]. Every technique offers specific structural data with different strengths and limitations and, in several cases, the combination of two or more techniques are used to compensate the limitations and enhance the strength of each individual technique. This work aims to compare the capacities of different techniques to provide 3D visualization and structural analysis of nanostructures, including the operation principles, advances, advantages and weaknesses of a large number of experimental techniques that are available and application areas with current examples. The methods presented include Scanning Probe Microscopy, Electron Microscopy, X-Ray Microscopy, with the combination of cryogenic technique and/or Focused ion beam approach. The presented analysis will allow one to understand better each technique, choose new ways of introducing these methods in a wide range of studies, assess them and identify the improvements that are still required. The advances made to date are reflected in the increase of structures registered in the PDB database. By 2021, the total number of structures available in the PDB database has reached 183 793 with an annual growth of 10 848. However, there are still challenges that must be overcome such as cost, scan time, sample preparation, and sample damage. Figure 1 summarizes the main characteristics of the 3D imaging techniques presented.

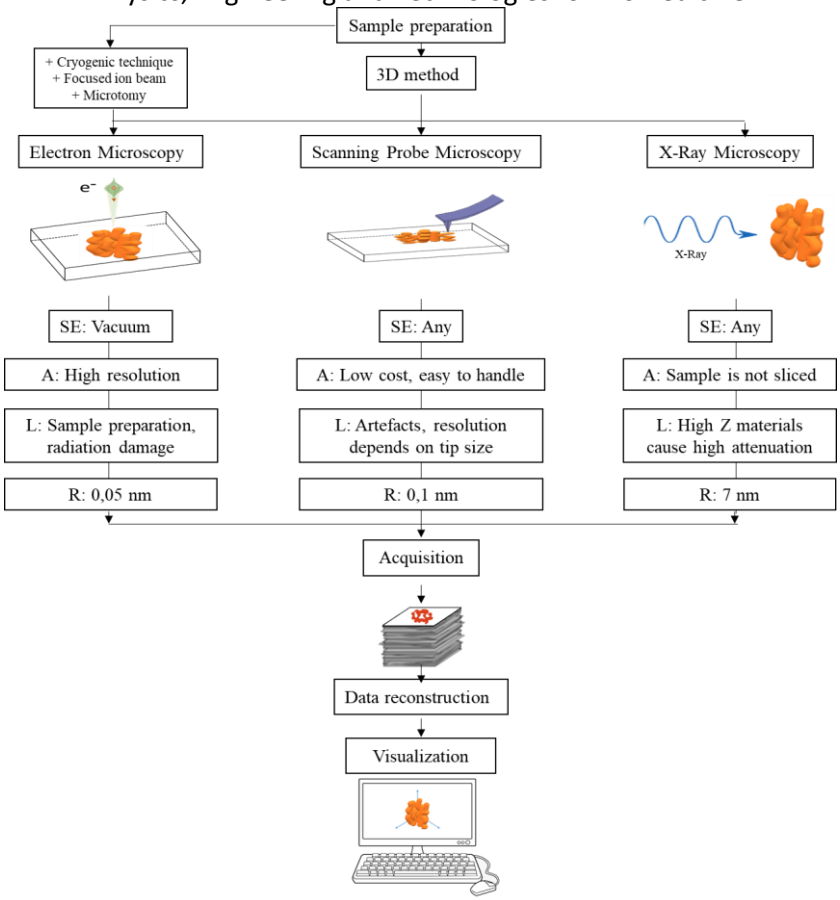

Fig.1. Electron microscopy, scanning probe microscopy and X-ray microscopy for 3D nanostructure analysis and visualization. SE: sample environment; A: main advantage; L: main limitation; R: resolution

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INFLUENCE OF POLYMER COATING ON COLLOIDAL STABILITY OF MIL-101 METAL-ORGANIC FRAMEWORKS

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Metal-organic frameworks (MOFs) attract a lot of attention in past decade due to their unique properties, such as high porosity and specific surface area which lead to high drug loading capacity. The cause of this is the nature of MOFs, as they are self-assembled hybrid organic-inorganic materials, containing high valent metals in nodes, which are linked by organic molecules.

MIL-101 MOFs can be built from trivalent Iron, Chromium or Aluminium and terephthalic or aminoterephthalic acids. In this work we studied colloidal stability of nano-sized MIL-101 based on aminoterephthalic acid and Chroimium metal clusters, denoted by MIL-101 (Cr).

Colloidal stability in physiological medium highly influences overall efficiency of drug delivery, as aggregated particles have smaller circulation time which lead to decrease of particles accumulation in targeted organ.

MIL-101 (Cr) rapidly lose their colloidal stability in phosphate-buffered saline by interaction with chlorine anions. In this work influence of different types of polymer coatings to aggregational stability of MOFs was studied.

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HEATING ABILITY OPTIMIZATION OF MAGNETIC NANOPARTICLES

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One of the promising methods of cancer therapy is magnetic hyperthermia [1]. This method is based on the ability of magnetic nanoparticles to convert the energy of an alternating magnetic field into heat to heat tissues to 42°C. For the effective and safe implementation of magnetic hyperthermia, it is necessary to use both optimized biocompatible magnetic nanoparticles (such as iron, magnetite, various ferrites), and moderate amplitudes and frequencies of an alternating magnetic field [1-3].

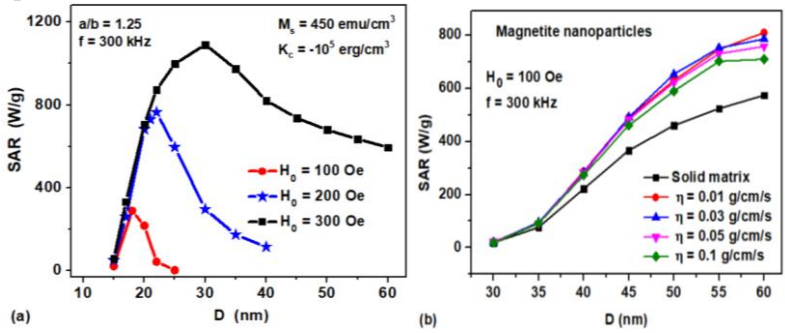

Fig.1. a) Dependence of specific absorption rate (SAR) of a dilute assembly of clusters of spheroidal magnetite particles with aspect ratios $a/b = 1.25$ on the transverse particle diameter $D = 2b$ at different amplitude of alternating magnetic field H_0; b) SAR comparison of magnetite nanoparticles dilute assemblies distributed in a solid matrix and in liquids with a viscosity $\eta = 0.01$; 0.03; 0.05 and 0.1 g/cm/s, respectively

In addition, heating sources have to be distributed taking into account possible complicated shape of a tumor [4].

In this work, using numerical modeling based on the stochastic Landau-Lifshitz equation, we calculated the SAR of iron and magnetite nanoparticles with cubic magnetic anisotropy distributed in liquid and solid media for various values of the field amplitude and frequency, particle diameters and aspect ratios (Fig 1a), and liquid viscosity (Fig 1b). To achieve the best therapeutic effect in magnetic hyperthermia, we also optimized the structure of the clusters of magnetic nanoparticles and investigated the optimal distribution of the heat sources in the media.

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ARRAYS OF SILICON NANOWIRES WITH DEPOSITED PLASMONIC NANOPARTICLES FOR SERS DETECTION OF BIOMOLECULES

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In recent years, silicon nanowires (SiNWs) have attracted research interest as a template for the surface-enhanced Raman scattering (SERS) due to their high surface-to-volume ratio, roughness at the nanoscale and tunability of the morphology [1]. However, the role of morphology of Si nanostructures for the effective SERS efficiency was not fully clarified.

Here we report a SERS analysis performed using Au-NPs deposited into SiNW arrays using a simple chemical deposition process. The ability of SiNW:Au-NPs substrates to enhance Raman scattering was appropriately evaluated using aqueous solutions of Methylene blue (MB) dyes with concentrations from 10^{-15} to 10^{-6} M. An effect of the morphology of SiNWs on the SERS efficiency was revealed and quantified.

SiNW arrays were formed on optically polished 350 μm-thick (100)-oriented c-Si wafers of p-type conductivity (boron-doped, specific resistivity of 1-10 Ohm×cm) by using the standard two-step MACE [2] with Au-NPs as the etching catalyst. The morphology and thickness of the prepared SiNW arrays were analyzed by using a Quanta 3D 200i Fei scanning electron microscope (SEM) and a JEOL JEM - 1400 Plus transmission electron microscope (TEM). The total porosity of SiNW arrays was estimated from the corresponding SEM images using a method of the box-counting [3]. The Raman spectroscopy studies were

carried out by using a Solver Spectrum Raman microscope (NT-MDT) with a HeNe laser excitation at 632.8 nm. The incident laser beam with an intensity of about 1 mW was focused down to about 10 μm diameter, and the accumulation time for each acquired spectrum was 10 s.

Fig. 1 shows that the sample of SiNWs:Au-NPs with 55 % porosity exhibits an increase in the SERS signal, which is several times larger than that for the samples with higher porosity.

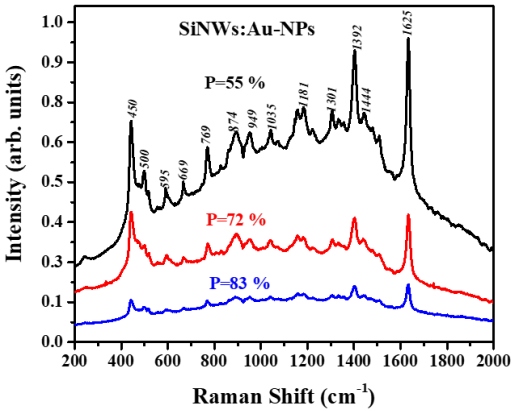

Fig.1. SERS spectra for SiNWs:Au-NPs arrays with porosity P= 55 % (black line), 72 % (red line), and 83 % (blue line) after deposition of MB (10^{-6} M).

By using the data shown in Fig. 1 the following values of enhancement factor (EF) of SERS were estimated for the samples SiNWs:Au-NPs: $6 \cdot 10^4$ (P=55%), $2 \cdot 10^4$ (P=72 %) and $1.1 \cdot 10^4$ (P=83 %), respectively.

The obtained results indicate that SiNWs with deposited Au-NPs are promising for biosensing applications.

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DELIVERY OF NANOPARTICLE COMPLEXES WITH MITOCHONDRIA

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A lot of nanoparticles are being developed for diagnostic and therapeutic purposes. One of the important problems in the field is the lack of in vivo delivery methods for nanodrugs. When entering the bloodstream, the particles are actively absorbed by immune cells before they could realize their function. We have developed a method for delivering nanoparticles on the surface of isolated mitochondria. The choice of this organelle for *in vivo* administration was due the fact that mitochondria are found freely circulating in the bloodstream.

Standard protocol [1] was used to isolate mitochondria from mouse liver and then organelles were incubated with different types of commercial magnetic particles for 30 min. Then unbounded particles were washed by centrifugation. Complexes of mitochondria and nanoparticles were incubated in blood plasma for desorption study in physiological-like conditions. Magnetometry [2] was performed to measure of bounded nanoparticles on the surface of mitochondria.

Mitochondria modified by fluidMAG-Chitosan (100 nm) nanoparticles were injected intravenously in mice. Concentration of circulating magnetic particles in blood and their biodistribution were measured by the magnetic spectroscopy approach. We show that chitosan-coated nanoparticles accumulate mostly in lungs. After that, the mitochondria were stained with DeepRed FM and injected in mice. Fluorescent tomography shown that the mitochondria accumulate in liver. We suggest

that the particles lose their connection with the mitochondrial surface due to friction in the capillaries.

So, isolated mitochondria can be applied for delivery of nanoparticles to lungs and potentially improve the therapy of diseases of the respiratory system.

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DYNAMIC 11C-METHIONINE AND 18F- FLUORODEOXY-GLUCOSE PET / CT IN THE STUDY OF BRAIN GLIOMA METABOLISM

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Purpose. The issue of determining the boundaries of the tumor is relevant, since in the case of an incorrect choice of the treatment volume the continuation of growth occurs precisely in the zone of infiltrative growth, unrecognized against the background of edema. The aim is to study of plastic and energy metabolism and their correlation with various histologic types of brain gliomas. Assessment of heterogeneity tumor structure and adjacent brain tissues by comparing MRI and ^{11}C-methionine (^{11}C-MET) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT data.

Materials and methods. 57 patients (M/F 31/26, average age 48±13 years) with gliomas: glioblastoma (n=20), anaplastic astrocytoma (n=11), diffuse astrocytoma (n=11), anaplastic oligodendroglioma (n=6), oligodendroglioma (n=9) were enrolled in this study. Research protocol consisted from MRI before and after contrast enhancement and dynamic ^{11}C-MET and ^{18}F-FDG PET/CT.

Quantification parameters were: tumor-to-normal ratio (T/N) at last 10 min of time-activity curve (an analogue of the routine index and reflects the activity of metabolic processes and), T/N in first peak of maximum uptake (Pmax) during first 60sec of study (reflects delivery level of radiopharmaceutical agent). Measurements were made in three areas: 1 – tumor core, 2 – edema/infiltration, 3 – intact brain tissue in close vicinity to the tumor borders (outside the T2-FLAIR hyperintensity zone). Comparison was made between areas 1 and 2, 2 and 3, and with

intact brain tissue reference; ^{11}C-MET and ^{18}F-FDG accumulation correlations were studied.

Results. Significant differences in T/N ^{11}C-MET between areas 1 and 2 were obtained in all gliomas ($p<0.05$). Pmax ^{11}C-MET differed only in glioblastomas ($p <0.0001$) and oligodendrogliomas ($p<0.05$), which correlated with the high level of vascularization of these tumor types. T/N ^{18}F-FDG significantly differed between area 2 and 3 ($p<0.05$), which might allow to evaluate the boundaries of infiltrative growth of glioma, with mandatory comparison with MRI. Strong stable correlations of plastic and energy metabolism (as well as high level of radiopharmaceutical agent delivery) in the core of astrocytomas (Grade II-III) ($Rs=0.8$, $p<0.05$) and edema/infiltration area around of glioblastomas ($Rs=0.5$, $p=0,02$) were found and proved the evolutionary theory of glioma growth.

Conclusion. Dynamic parameters can improve the quality of differential diagnosis of tumors in PET / CT studies with ^{11}C-MET and ^{18}F-FDG. The patterns of ^{11}C-MET /^{18}F-FDG distribution as well as plastic and energy metabolism correlations in different tumor areas (core and edema/infiltration) and intact brain tissue in close vicinity to the tumor borders bring us closer to understanding the fundamental metabolic processes of brain gliomas.

SILICON-IRON NANOPARTICLES PREPARED BY LASER ABLATION FOR BIOMEDICAL APPLICATIONS

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Over the last decade, there is a constantly growing interest in using nanoparticles (NPs) for biomedical applications [1]. Silicon (Si) NPs have attracted attention for biomedical applications due to their low toxicity and biodegradability. For example, Si-NPs have been shown to be excreted from the mice body through renal clearance within few weeks [2]. Iron (Fe) based NPs were actively studied because of their excellent physical properties such as high saturation magnetization and high magnetic susceptibility. They can be used for numerous biomedical applications such as magnetic resonance imaging (MRI) contrast enhancement, magnetic hyperthermia, drug delivery, etc. [3].

In this work, we have synthesized composite Silicon-Iron (Si-Fe) NPs by laser ablation and investigated the obtained NPs for biomedical applications as potential contrast agents in MRI.

Si-Fe NPs were synthesized by femtosecond laser ablation of Si and Fe-silicide mixed target in a quartz vessel filled with distilled water. The laser ablation was done by femtosecond Yb: KGW laser (Avesta, Teta 10, Russia) with 1030 nm wavelength, pulse repetition rate from 1 to 100 kHz and pulse energy up 100 μJ for 30 minutes. NPs were investigated by means of the transmission and scanning electron microscopies (TEM, SEM), X-ray fluorescence (XRF), X-ray diffraction, dynamic light scattering (DLS) and NMR Relaxometry.

TEM, SEM images and DLS data demonstrate that the prepared NPs are mostly spherical with mean diameters ranging from 20 to 220 nm. According to the XRF analysis the prepared NPs contain from 10 to 25 at. % of Fe in silicide and oxide forms. Figure 1 shows typical transients of the longitudinal and transverse proton magnetization in suspensions of Si-Fe NPs with 25 at. % of Fe. The magnetization transients reveal strong shortening of the relaxation times. The relaxivity values for the longitudinal and transverse proton magnetization are r_1= 0.9 $Lg^{-1}s^{-1}$ and r_2 = 16.4 $Lg^{-1}s^{-1}$, respectively. The obtained high relaxivities of the prepared NPs demonstrate their potential for applications as contrast agents in MRI diagnostics of cancer.

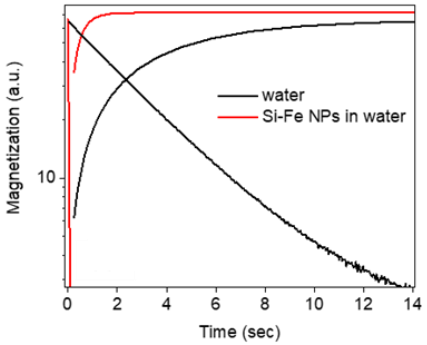

Fig. 1. Transients of the longitudinal and transverse proton magnetization in pure water (black lines) and in aqueous suspensions of Si-Fe NPs (red lines)

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CYTOCOMPATIBLE APPROACH FOR CREATING PORES IN SCAFFOLDS

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Extrusion based bioprinting with hydrogels is an important and demanded tool in tissue engineering [1]. To date, one of the main limitations in the design of large (more than 5×5×5 mm), suitable for replacement of tissues and organs of tissue-engineered grafts, is considered to be insufficient access of oxygen and nutrients inside the finished structure [2].

The aim of this study was to create scaffolds by extrusion based bioprinting with a two-component hydrogel that forms a pore structure during cultivation.

Bioprinting was carried out Rokit 4D bioprinter (Invivo, South Korea) with software version 1.68. Slicing of the model was carried out in NewCreatorK program version 1.57.63. The printing speed was 5 mm/s. The dispenser temperature was set at + 4 °C. The printing table was at room temperature. Printing was carried out in sterile Petri dishes (Corning, USA). Bioinks were prepared on the basis of sterile type I pig atelocollagen (80 mg / ml, Imtek, Russia) with the addition of gelatin (Sigma-Aldrich, USA) 100, 25 and 6.25 mg / ml. Scaffolds were printed in the form of cubes measuring 4 × 4 × 4 mm. Immediately after printing, the objects were flooded with a warm (+37°C) medium. Composition of the medium: RPMI-1640 (PanEko, Russia) with the addition of penicillin-streptomycin (PanEko, Russia) at 50 units / ml and 50 μg / ml. The printed scaffolds were incubated at + 37 °C and 5% CO_2 for 3 days.

To study cytocompatibility, constructs with MSC culture (0.89×10^6 per ml) were printed. We studied two groups of scaffolds: solid collagen

(4%) and collagen with the addition of 6.25 mg / ml gelatin (300 Bloom). The finished scaffolds were poured with nutrient medium DMEM (serum, glucose 1 g/L, PanEco, Russia) and incubated. After 1, 3, 7 and 14 days the objects were poured with a collagenase solution (0.15 mg / ml) in a DMEM nutrient medium (without serum). A day later, cells were taken from the culture dish, cells were centrifuged (400G for 3 minutes) and counted in a Goryaev's chamber using an inverted microscope Biomed-3 (Russia). The resulting scaffolds were fixed for 24 h in an acidic Buena liquid (including 1.3% trinitrophenol (Sigma-Aldrich), 40% formalin (BioVitrum, Russia). After washing in 70% ethanol, the standard histological preparation of the samples was performed with their subsequent imprisonment in a paraffin medium (Histomix (BioVitrum, Russia) Paraffin sections 5 μm thick, obtained on a microtome (Leica RM2235, Germany), were placed on silanized glasses (S3003, Dako, USA). The percentage of porosity and pore diameter were calculated using ImageJ software version 1.52a. of the obtained slices.

Pores were formed due to the washing out of the pore-forming component of bio-ink during incubation. The maximum percentage of porosity was 15.974 ± 1.446 for gelatin granules (300 Bloom) with a concentration of 100 mg / ml, the minimum 2.901 ± 0.391 for gelatin granules (90-110 Bloom) with a concentration of 6.25 mg / ml. The values obtained are in excess of the control sample ($1.826\% \pm 0.292\%$) of collagen ink. The doubling time of the MSC culture embedded in porous structures was 1.79 ± 0.13 days, for solid structures this indicator is 2.43 ± 0.37.

This approach makes it possible to create scaffolds with a high level of porosity and cytocompatibility, which is realized in the process of extrusion 3D bioprinting.

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STUDY OF THE EFFECTS OF THE COMBINATION OF CEFTRIAXONE AND LIDOCAINE IN THE IN VITRO EXPERIMENT IN THE CULTURE OF MICROORGANISMS

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The drug of choice in the treatment of inflammatory diseases caused by opportunistic microflora is ceftriaxone [1]. Ceftriaxone is a parenteral third-generation cephalosporin with high activity against gram-positive and gram-negative bacteria. To reduce the intensity and frequency of pain at the injection site with the introduction of ceftriaxone, it is often used jointly with 1% lidocaine solution [2]. Lidocaine is a short-acting local anesthetic of the amide type. Effective for all types of local anesthesia. Expands blood vessels. Does not irritate fabrics. Pharmacokinetic data have shown that 1% lidocaine does not affect either the excretion parameters or the bioavailability of intramuscular administration in combination with ceftriaxone [3]. The paper presents the results of a study of the effects of a combination of ceftriaxone and lidocaine in an in vitro experiment in a culture of microorganisms. The formation of antibiotic resistance of bacterial cultures of pathogenic staphylococci and Escherichia coli to ceftriaxone in combination with lidocaine was studied. A comparative assessment of the antimicrobial action is given. in vitro cephalosporin and test drug combinations. The influence of irrational antibiotic therapy on the formation of resistant strains was also studied.

Studies by the disk diffusion method have shown that in vitro in the culture of pathogenic staphylococci and Escherichia coli, ceftriaxone is effective and has a pronounced antibacterial effect in 90% of cases. Only 10% of bacterial strains showed antibiotic resistance.

The study of the antibacterial properties of lidocaine in vitro in the culture of bacteria by the disk-diffusion method showed that the local anesthetic does not exhibit antibacterial properties.

Evaluation of the combined use of ceftriaxone and lidocaine preparations in vitro in bacterial culture by the disk diffusion method showed a pronounced decrease in antibiotic sensitivity of bacteria (40%) of cases. The diameter of the growth retardation zone, in the study of pathogenic staphylococci, decreased in comparison with the effect of ceftriaxone alone (60%).

A similar dilution of ceftriaxone with lidocaine and ceftriaxone with distilled water showed that dilution with lidocaine increased the growth of S. aureus by 10%.

Thus, the combined use of ceftriaxone with lidocaine can lead to a decrease in its antibacterial efficacy in vivo when administered intramuscularly.

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CARBON DOTS SYNTHESIZED BY GREEN SYNTHESIS

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Carbon dots(CD) is a type of nanomaterials that have small size, low toxicity and lumeniscence. Their features make them perspective for wide spectre of applications – bioimaging, biosensing, optoelectronics, catalysis etc. Because of their low toxicity, small size and adjustable spectre of luminescence they are especially perspective for biomedical applications, in particular bioimaging, tumor therapy, drug delivery [1]. Another advantage of carbon dots is simple, cheap and quick synthesis, they can be made from cheap sources of even biological wastes. In our study we tried synthesizing CD from urea and citric acid using microwave reactor. This method is quick (10 minutes), ingridients are very cheap, also this method allows adjusting of the spectre of luminescence by changing the ratio of ingridients and temperature [2]. Red emitting CD are most perspective for biological application as red light has long wave and good permeability into tissues [3]. For synthesis we took 0,5 gr of urea and 0,5 gr of citric acid, added 4ml of distilled water and put it into microwave reactor for 10 minutes and set temperature 180 C. Acquired particles emitted blue in ultraviolet and red in green light. Further study include purifying the particles and making biotests on cellular models and tumor models.

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SIZE-SELECTED SILICON NANOPARTICLES WITH MIE RESONANCE FOR PHOTOHYPERTHERMIA

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Pure silicon (Si) nanoparticles (NPs), due to their low toxicity and biodegradability, are widely used in bioimaging, therapy, and biosensorics [1]. There are many different applications for solving the Mie scattering problem for spherical NPs in lasers and quantum optics, optical spectroscopy techniques, optoelectronics and quantum information [2]. As for Si NPs, it was shown by 3D simulation that irradiation by pulsed laser can form a region with a maximum temperature exceeding 42°C, which is the temperature of muscle tissue protein denaturation [3]. However, there have been no studies of the enhancement of light absorption by spherical NPs under the influence of resonant wavelengths and the associated overheating.

In our work aqueous suspentions of Si NPs were prepared by femtosecond laser ablation of crystalline Si wafers immersed in distilled water. To select NPs by size, an aqueous solution of NPs was subjected to repeated centrifugation with precipitation and sonication to separate the formed agglomerates and improve the selection efficiency. Depending on the number of centrifugations, it was possible to narrow the spread in NP sizes and shift the peak from the green wavelength range (520-550 nm) to the long-wavelength region of the spectrum (up to 630 nm).

The heating of aqueous solutions of Si NPs at various concentrations was checked using a thermal imaging camera. To meet the conditions of those in biological systems, the temperature of the solution was set constant at about 36-37 ° C using a thermostat. We used lasers with wavelengths of 528 nm and 667 nm, pulsed and continuous wave (CW), powers of 60 mW. The results demonstrated an increase in the temperature of solutions with Si NPs up to 13 ° C in comparison with water in the same thermostat. The heating rate was maximum for cases of irradiation with a pulsed laser with a wavelength corresponding to the position of the resonance peak of NPs and decreased for cases of non-resonant irradiation.

In vivo experiments were also carried out to irradiate biological objects of *Paramecium Caudatum* with lasers of wavelengths corresponding to the Mie resonance of Si NPs placed inside organisms. The luminescence of NPs in cell cavities was observed under a microscope in reflected light and demonstrated some shift of the resonance wavelengths to longer wavelengths. The pulsed regime in the wavelength range resonant for Si NPs is found to be more efficient, leading to complete cell destruction even under relatively mild laser irradiation conditions.

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FABRICATION AND CHARACTERIZATION OF CHONDROSPHERES AS BIOMATERIALS FOR 3D BIOPPRINTING OF CARTELINE TISSUE IN TREATMENT OF CARTELINE DEFECTS

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The development of technologies for effective restoration of damaged cartilage tissue is an important goal of regenerative medicine. To solve this problem, three-dimensional bioprinting can be used, which makes it possible to create tissue structures that resemble native tissues. When spheroids from primary human chondrocytes are used as bioink, fabricating tissue structures of cartilage, repeating the shape, structure and architecture of a cartilaginous defect, is possible. [1-2]. In this work, the fabrication and characterization of human chondrospheres was carried out with the aim of their subsequent use for the regeneration of cartilage defects.

Spheroids from primary human chondrocytes were formed using agarose forms (MicroTissues 3D Petri dish, USA), we were using several cell concentrations: 1000, 3375, 8000, 16000, and 27000 cells / spheroid. The kinetics of spheroid growth was studied for 14 days. For all concentrations, the formation of spheroids of the correct shape of approximately the same size was observed within the same concentration. In the process of cultivation, a gradual decrease in the diameters of the spheroids took place (Fig. 1).

The kinetics of fusion, spreading, as well as the biomechanical properties of chondrospheres were studied. All spheroids demonstrated complete fusion within 24 hours, effective spreading, and also increased mechanical strength during cultivation.

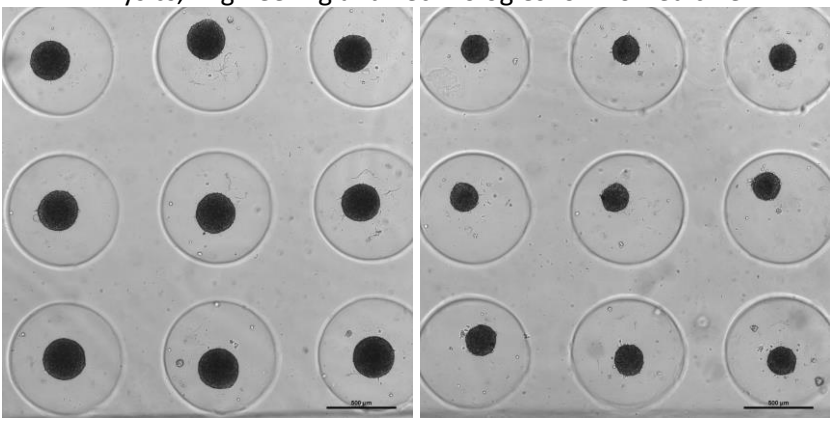

Fig.1. Chondrospheres at a concentration of 8000 cells / spheroid on 2 day (left) and on 6 day (right) of cultivation. Scale 500 μm

Next stages of the study include finding the optimal concentration of chondrospheres, to form spheroids of the maximum possible diameter, allowing the penetration of oxygen and nutrients into the center of the spheroid due to passive diffusion. Then spheroids will be used to heal cartilage defect with 3D printed tissue.

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CREATION OF TISSUE-ENGINEERING CONSTRUCTS OF VARIOUS SHAPES USING MAGNETIC PATTERNING OF SPHEROIDS

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Magnetically directed patterning is a promising direction of tissue engineering based on magnetic fields as temporary or removable support in assembling biological structures from individual cells, cell monolayers and spheroids [1, 2]. Recently, polymer microcapsules loaded with iron oxide nanoparticles have been proposed as a novel approach to designing magnetic materials with high local concentrations [3].

In this work, we formed tissue-engineering constructs of linear, branched and circular shapes using magnetic patterning of spheroids from the murine fibroblast cell line NIH3T3 (Fig. 1).

Magnetic capsules containing iron oxide nanoparticles in concentrations of 12 and 20 microcapsules per cell were used to magnetize the cells. The microcapsules demonstrated an inconsiderable toxic effect on NIH3T3 cells which retained the typical morphology of fibroblasts.

Tissue spheroids from magnetized NIH3T3 cells were successfully formed. Magnetic capsules did not affect the fusion kinetics and viability but increased the biomechanical properties of spheroids. The magnetic spheroids were placed in Petri dishes with neodymium magnets underneath. Rapid assembly of spheroids and their patterning according to the shape of neodymium magnets was observed. After 24 hours, there was a partial fusion of the spheroids and the formation of tissue con-

structs, which retained their shape and integrity after removing the magnet. After 5 days, the spheroids completely fused and formed tissue constructs without volume defects or empty spaces.

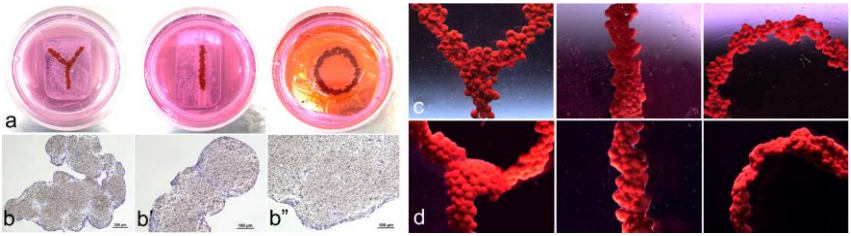

Fig.1. Formation of branched, linear and circular constructs by magnetic patterning of tissue spheroids labeled with 12 magnetic microcapsules per cell. a – photographs of magnetic patterning of spheroids; b-b" – histological examination of circular tissue constructs demonstrating advanced stage of tissue spheroids fusion. Samples were stained with hematoxylin and eosin; stereo images of tissue constructs formed from magnetic spheroids during 24 hours (c) and 5 days (d).

Thus, in the present work we have demonstrated the effective uptake of iron oxide nanoparticles in polymeric capsules by cells and their low cytotoxicity. Magnetic capsules labeled cells were used for fabrication of tissue spheroids with evident magnetic properties. Strong magnetic properties of labeled tissue spheroids enabled their successful magnetic patterning and formation of tissue constructs of various shapes.

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WEAK LIGHT-MATTER COUPLING IN NEAR-INFRARED LUMINESCENT SYSTEMS BASED ON FREESTANDING POROUS SILICON MICROCAVITIES EMBEDDED WITH PBS QUANTUM DOTS

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Hybrid photoluminescent (PL) structures operating in the near-infrared (NIR) region of transparency of biological species attract great attention for applications. Of particular interest are systems in which the light-matter interaction can be observed [1]. The systems based on luminophores embedded into a microcavity (MC) may exhibit PL enhancement in the weak coupling regime, while formation of new hybrid energy states in the strong coupling regime may also occur. These effects permit obtaining Bose-Einstein condensates, increasing conductivity, enhancing Raman scattering and creating new sensing systems, etc. [1,2].

We have manufactured hybrid PL structures based on PbS quantum dots (QDs) and porous silicon microcavities (pSi MCs) operating in the NIR region of optical spectrum. The MCs were fabricated by electrochemical etching of monocrystalline Si and composed of top and bottom Bragg mirrors consisting of alternating pSi layers of low and high porosities, with a cavity layer between them. The MCs were detached from Si substrate by electrochemical polishing what resulted in a 100-nm blueshift of their reflectance spectra whereas the eigenmode width and Q-factor (10 nm and 200, respectively) remained the same. The MCs were thermally oxidized to stabilize their optical properties and to minimize the number of non-radiative recombination channels for QDs excitons, what provoked a further blueshift of the reflectance spectrum and a broadening of the eigenmode. Finally, QDs were embedded into pSi

MCs by drop-casting. The PL spectrum of the hybrid structure was narrowed as compared with the QDs solution (Fig.1) what is explained by an enhancement of QD PL within the MC by Purcell effect [3], an indicative of weak coupling established between the MC eigenmode and QD excitons. Thus, our hybrid PL structures operating in the NIR region demonstrated weak light-matter coupling what paves the way to design of new sensor systems suitable for biological applications and capable of continuous operation by pumping analytes through the freestanding MC-QD sensing system.

This work was supported by the Russian Foundation for Basic Research grant no. 18-29-20121, and by the Russian Science Foundation grant no. 21-79-30048 in its part related to pSi microcavities engineering.

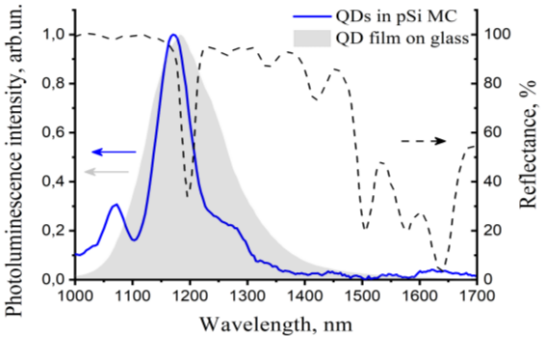

Fig.1. PL spectra of QDs in a pSi MC (blue) and QD film on glass (grey); the dashed line indicates the MC reflection spectrum

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DELIVERY OF MEDICINES USING MAGNETIC NANOCONTAINERS

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The treatment of cancer in the 21st century remains one of the most important topics for a person, the modern works of the authors and the information obtained from them have greatly advanced in this direction and open up a wide range of directions for a person in which the most effective movement is possible to obtain the best result in solving this problem.

The characteristics of heating under the action of an external alternating magnetic field depend on the physicochemical characteristics of magnetic nanoparticles, which affect the magnetic properties, relaxation processes, and hysteresis losses. The characteristics of magnetic hyperthermia of nanoparticles are influenced by such characteristics as: chemical composition, their structure, sizes of magnetic nuclei, particle sizes and properties of the medium in which the particles are dissolved, as well as the frequency and amplitude of the generated magnetic field [1].

The setup for the first experiment consists of a cell with a suspension containing magnetic particles (magnetic fluid based on dextran or glycerin), a temperature measurement system (thermocouple connected to a multimeter) and a generation system, as well as magnetic field control (coils, connecting wires, laboratory source power supply with the ability to adjust the voltage and current). Rheopolyglucin was initially chosen as the basis for the magnetic fluid. Induction heating experiments were carried out on samples using this base.

Additional experiments were performed using glycerin. This decision was motivated by the desire to increase the viscosity of the solution obtained for the experiment and to increase the settling time of the particles, which made it possible to increase the time of exposure to the

magnetic field by a significant amount of time in the experiment. In the first experiment, the coils were supplied with a sinusoidal voltage with an amplitude of 2 - 15 V at a current of 5 A from a generator of an alternating power source. AC frequency - 50 Hz. Temperature measurements were carried out using an ETP-02A thermocouple designed for operation in the range of -50 ... + 400 ° C connected to a multimeter. Samples of magnetic fluids were placed in an alternating magnetic field. The experiments were carried out in a room with low humidity at a temperature of 25 degrees Celsius, which excluded the side effect of the environment on heating.

As a result of the studies carried out using two parallel-connected coils and a magnetic fluid based on dextran, it was not possible to heat the particles at a given voltage and current strength, in the case of the second experiment carried out using a magnetic fluid based on glycerin, the result was small - 1-1,5 degrees Celsius. When using the maximum possible parameters of the experimental equipment, due to the higher viscosity and particle settling time (260 seconds), the best result was obtained.

Experiments carried out in practice show their possible effectiveness; in the planned experimental study, taking into account the previous experience, it is planned to increase the power of the magnetic alternating field and reduce the size of the obtained ferrite nanoparticles by chemical coprecipitation or by the sol-gel method. This will increase the settling time of particles in the liquid and make the particle size more evenly distributed in size, which, in turn, will increase the heating of the resulting magnetic fluid and increase the therapeutic and delivery effect of this method.

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LASER CORRECTION OF PbSe CHALCOGENIDE FILMS PHOTOSENSITIVETY

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The study is aimed at increasing the photosensitivity of PbSe chalcogenide films in a narrow spectral range. It was proposed to investigate the mechanisms of laser modification of chalcogenide films. To develop a technique for assessing the quality of modified regions of PbSe films with a thickness of 1 μm, measuring their optical characteristics [1].

Such films have a high absorption capacity in the mid-IR range (1 - 4 μm), which is used in the photodetection of organic molecules in the form of a gas mixture or liquid. In this case, the optical properties of the semiconductor film and its photoelectric parameters become extremely important characteristics. Changing these properties and correcting them in small ranges of values is a very promising task for many applications. For example, optoelectronic systems, solar cells, and LED technology as photoelectric sensors. In recent years, research group [2] have studied the structure and optical properties of AlZnO:Ag semiconductor films before and after its laser modification.

Modification of the film structure by continuous laser radiation is promising for many new applications in photonics [3]. Local laser exposure initiates a photothermochemical mechanism for modifying the film structure, which is important to control. Optical methods of control over laser modification of films will allow non-contact and real-time tracking of all changes.

In this work, the result of laser action on PbSe films in the scanning mode with continuous radiation with a wavelength of 405 nm was investigated (Fig. 1). As a result of photothermal action on the structure of the film, its reflection and transmission changed in the spectral range of 0.3 - 1.0 μm. At a power density of 121.6 W/cm^2, photobleaching of the material and its melting were observed, followed by destruction, leading

to the formation of microcracks. With a decrease in the power density to 76 W/cm^2, a photodarkening of the film was observed in the region of laser action (Fig. 2). For the modified sections of the film, in this case, a sharp decrease in transmission and reflection was observed, and in its optical characteristics it approached a dark body.

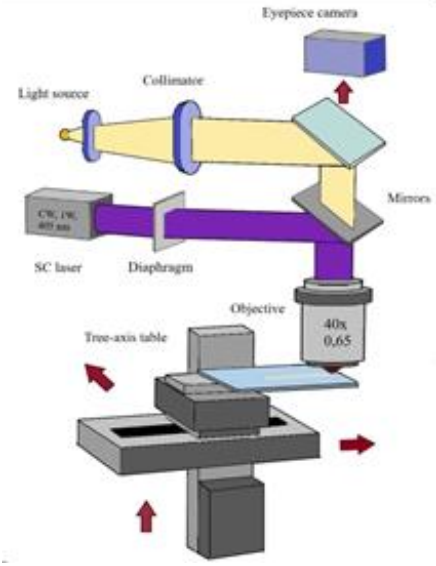

Fig.1. Scheme of an experimental setup for laser modification of PbSe films

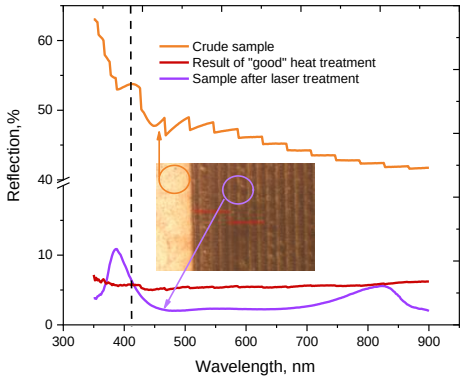

Fig.2. Reflection spectra obtained for samples subjected to various treatments: (1) crude sample, (2) result of "good" heat treatment, (3) sample after laser treatment. Also figure shows tracks obtained by laser processing on a raw sample

The study is funded by the grant of NIRMA (2021).

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NANOSILICON-BASED RNA DELIVERY SYSTEM WITH ENHANCED CAPACITY FOR siRNA THERAPY

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Small interfering RNA (siRNA) is a class of nucleic acid-based drugs able to interact with mRNA before its translation and block gene expression. This can be useful in therapy of various diseases. There is a problem, however, with siRNA intracellular transport. RNAs cannot cross cell membranes because of the large size and negative charge. They undergo rapid degradation by plasma enzymes and easily subjected to fast clearance. So, it is necessary to develop methods of delivery systems for siRNA that will have specific properties, such as biodegradability, low toxicity, high loading capacity.

One of the recent innovations in the field of delivery of therapeutic drugs is Silicon nanoparticles carriers (SiNPs). They are relatively harmless to the human body due to their mild decomposition to silicic acid excretable by the kidneys. From the variety of SiNPs manufacturing methods, we chose laser ablation-made SiNPs for further surface modifications. They have, among others, stronger surface structure and more uniform size distribution[1].

For introduction of anion-exchange properties, the SiNPs were treated with 2'-aminoethyl-3-aminopropyltrimethoxysilane (AE-APTMS). Then NPs were tested for loading capacity with a standard RNA sample. As the anion-exchange capasity is dependent both on surface hydroxylation extent of NPs and amine-ammonia equilibrium, three methods of surface modification were compared. SiNPs were manufactured in the deionized water (1, figure 1), 15% H_2O_2 (2,3), all processed with AE-APTMS, and, in the latter version, amino-coated SiNPs were mixed with methyl iodide and pyridine to form quaternary ammonium salt. According to our results, the second approach to the modification of SiNPs proved the best loading of siRNA onto nanoparticles surface. The

data obtained are shown in the figures below. Surprizingly, quaternary ammonium carrier had shown lower performance, probably due to an increased ionic radius.

RNA release rate was quite similar in all cases, 50-60% of the loading was released during first 6 hours.

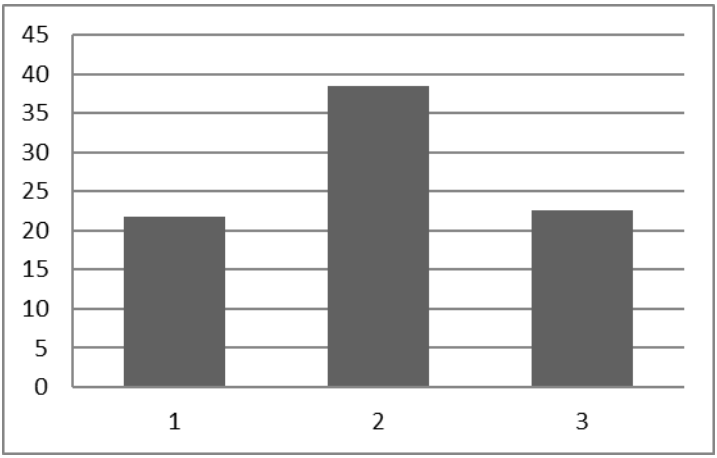

Fig.1. Total RNA loading capacity (wt/wt percentage) of SiNPs with different surface modifications

We obtained excellent loading capacity and desorption rate, exceeding results of recent study of other modifications.

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MODEL FOR DETECTING STRUCTURELESS AREAS IN IMAGES OF SKIN NEOPLASMS IN THE DIAGNOSIS OF MELANOMA IN ONCODERMATOLOGY

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The characteristics of skin melanoma are a high potential for metastasis, a high mortality at the late stages of the disease and an increase in the morbidity rate in the world today [1]. The use of information technology provides intellectual support to a dermatologist in improving the accuracy of the diagnosis of melanoma [2]. An important sign of melanoma is the presence of structureless areas in the dermatoscopic image of a skin neoplasm [3].

The aim of the present study is the calculation of the optimal variance filter parameters (the window size N and the variance threshold value T) for the model of structureless hypopigmented areas recognition [4] using extended image sample. For the study, we used 99 digital images of skin neoplasms of different brightness and contrast, and containing different structures (dots, globules, pigment networks, etc.) of various sizes, brightness and contrast. To calculate the accuracy, we used the formula (1), where TP is "true positive", FN – "false negative", FP – "false positive".

$$Accuracy = \frac{TP}{TP+FN+FP} \qquad (1)$$

Results

The best accuracy was obtained with N = 10, T = 11 (Accuracy = 87.5%) and N = 15, T = 15 (Accuracy = 87.5%) (Fig.1).

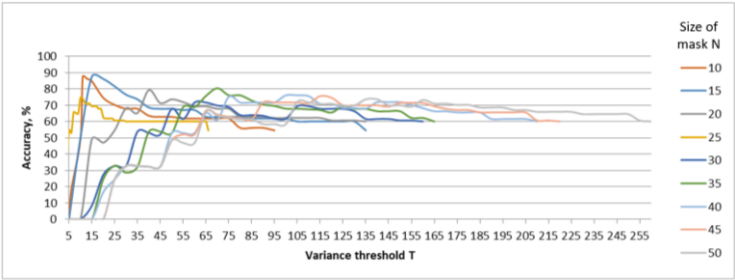

Fig.1. Accuracy of recognition of hypopigmented structureless areas at different values of the variance filter parameters

When the window size N is less than 10, the accuracy drops sharply. Increasing the size of the window increases the duration of image processing. The larger the window size N, the larger the optimal value T for the variance threshold.

Conclusions

The obtained results of the work will make it possible to analyze the existing model of recognition of hypopigmented structureless areas for the possibility of modifying the model in order to increase the accuracy of its work. Another application of the work results can be the use of a dispersion filter in models for recognizing structureless areas of other types (hyperpigmentation zones, white-blue veils, etc.).

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A MONTE CARLO SIMULATION OF BORON PROTON CAPTURE REACTION IN THE FRAMEWORK OF THE USE IN RADIATION THERAPY

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Proton therapy is a modern and extremely accurate modality of radiation therapy. The development of accelerator technologies in recent decades has made it possible to transfer proton therapy from research centers to full-fledged clinical practice. The fundamental benefits of proton therapy allow for an increased target dose, resulting in improved tumor control without increasing radiation toxicity to surrounding healthy tissues. However, in some cases, proton therapy fails to treat radioresistant tumors. In these cases, the use of heavier ions is required. Therefore, in recent years, Proton Boron Capture Therapy (PBCT) has received more attention and research because it is a potential method that can increase the biological effectiveness of Proton therapy in cancer treatment. It is possible to overcome the radiation resistance of cancer due to a significant increase in the complexity of DNA damage due to increase linear energy transfer (LET), that is, a higher relative biological efficiency (RBE).

However, the debate about the effectiveness of this method has not ended. On the one hand, Yun et al. It has been shown that PBCT can increase the dose at the peak of Bragg protons by more than 1.5 times if boron accumulates in tumor tissues [1]. In addition, Cirrone et al. reported the results of in vitro irradiation of prostate tumor cell samples with and without boron. And it was shown that the presence of boron in concentrations of several tens of ppm leads to a decrease in the probabil-

ity of cell survival [2]. On the other hand, Annamaria Mazzone et al. objected and pointed out that the reaction of proton synthesis with boron is not the main reason for the decrease in cell viability in the presence of boron [3].

Therefore, the aim of this work is to assess the dose of PBCT compared to conventional proton therapy using the Monte Carlo method to assess the effectiveness of this method. In particular, the use of TOPAS software to simulate the interaction of boron particles and accelerated proton beams. It is believed that alpha particles with high LET, which are created in this interaction, are responsible for increasing the dose and decreasing the probability of survival of tumor cells [2-4].

In this work, calculations and Monte Carlo simulations show that there is a small dose-dependent increase in this response at clinically acceptable concentrations, i.e., less than 100 ppm compared to the dose delivered by the primary proton beam inside the target. This small increase does not yet indicate the superiority of the method in enhancing the therapeutic effect of proton therapy. However, a statistically detectable effect was recorded from alpha particles produced by interaction with protons with boron. Thus, a preliminary conclusion can be drawn that the proton reaction of proton capture by boron can play a significant role in reducing cell viability. And for a more accurate assessment in future studies, we will assess cell viability through experimental studies.

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MICRORNA SENSING USING DNA-TEMPLATED SILVER NANOCLUSTERS

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Metal nanoclusters are small particles with unique electro-optical properties consisting of 2-10^2 atoms. The most common matrices for the synthesis of silver nanoclusters are DNA oligonucleotides. Fluorescent properties of silver clusters depend on the DNA stabilizing matrix. Fluorescent nanoclusters are widely used in various fields of science due to the simplicity of synthesis. At the moment, the most promising field of application of precious metal clusters is bioimaging and biosensing [1]. Nanostructures are also used for the detection of biopolymers, in particular, nucleic acids.

In this work, we developed a sensor for detecting microRNAs. MicroRNA is a small RNA molecule about 20 nucleotides long. Changes of the expression of these molecules in body fluids occur earlier than changes found in other currently known biomarkers, which makes it easier to diagnose such diseases as cancer or Alzheimer disease as quickly as possible [2]. Extracellular (circulating) microRNA can be detected in various biological fluids, for example, in blood plasma or in follicular fluid. In this regard, the development of a sensor for the detection of this molecule can simplify the procedure for the diagnosis and treatment of various diseases.

The developed sensor emits fluorescent light only by interaction with the target. The sensor model logically divided into three parts: a hybridization sequence, that complementary to the target, a NC-scaffold sequence, which forms the cluster and a spacer: it links these two parts together. The optimization of a spacer sequence showed that the best optical parameters of a silver nanocluster were obtained with the spacer of one adenine on each matrix strands. The DNA analog (5'-CTGTGCGTGTGACAGCGGCTGA-3') served as a model target of mir-210. The sensor was successfully tested with DNA – target. It

showed bright green fluorescence with excitation/emission at 490/560 nm, which appeared only in the presence of target. The target detection limit (LOD) was determined as 3 nM. The proposed model can be used for the detection of other nucleic acids.

Acknowledgments: This work was supported by RFBR grant № 19-53-51005.

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[GABA] CONCENTRATION IN POSTERIOR CINGULATE CORTEX AFTER ACUTE PEDIATRIC CONCUSSION

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Introduction

Concussion or mild traumatic brain injury (mTBI) is one of the most widespread types of trauma. The literature data on the [GABA] change after acute mTBI is based on the measurement of GABA+ levels, where GABA signal is contaminated with macromolecular (MM) compound. The aim of this study is to measure GABA- in the posterior cingulate cortex (PCC) cerebral region in the acute phase of mTBI in children.

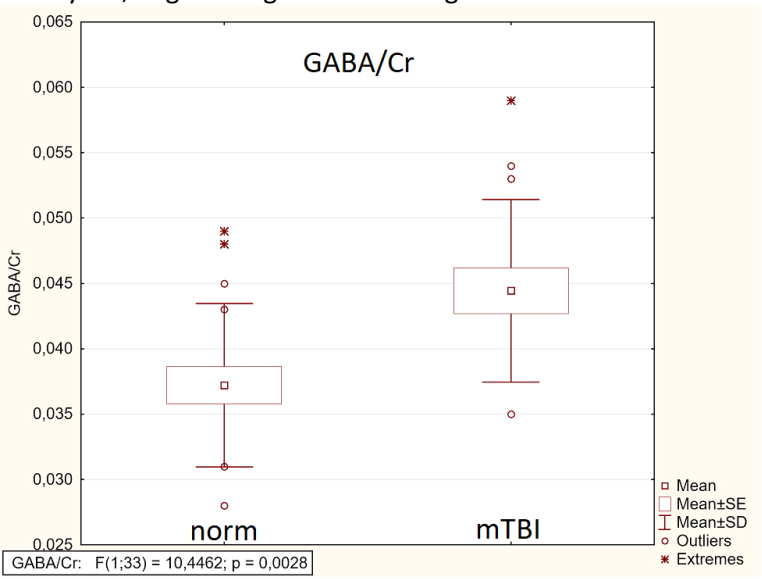
Materials and Methods

Nineteen patients with acute mTBI (12-70 hours since the injury, 16.2±1.4 y.o.) and twenty-one healthy control (18.5±2.3 y.o.) participated in the study. Philips Achieva 3.0T was used, standard MRI protocol for TBI patients revealed no pathological lesions in brain tissue of any subject. MRS voxel (50x25x25 mm) was located in PCC. MEGA-PRESS pulse sequence without MM contamination was used: TR = 2000 ms, TE = 80 ms, 180-editing pulses applied on 1.9 ppm and 1.5 ppm, NSA = 288 (acq. time ~10 min). Spectra were processed in Gannet 3.1, [GABA] and [Glx] values were calculated.

Results

[GABA] was statistically significantly higher (by 12%, p=0.036) in mTBI group than in the normal group, while [Glx] was unchanged.

No correlation between the metabolite levels and age was revealed in both groups.



Discussion

Previously we have demonstrated that GABA-/Cr increases in anterior cingulate cortex of children with mTBI. To our knowledge, the increase in GABA- in PCC in current study is reported for the first time. The lack of correlations between age and metabolite levels agrees with the literature data and eliminates possible bias of the results caused by group age difference.

This study provides insight into metabolic alterations caused by mTBI and may facilitate better understanding of the long-term mTBI consequences.

MATHEMATICAL MODELING OF GLYCOGEN STORAGE PROCESS IN HEPATOCYTES

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Proper insulin signaling in hepatocytes provides living organisms with metabolic flexibility by keeping plasma glucose concentration stable in fasting and postprandial states. The shift between the states is regulated by a switch from glucagon to insulin signaling and occurs in a calcium-dependent manner on the intracellular level [1].

One of the essential processes in plasma glucose regulation in hepatocytes is glycogen synthesis, occurring in a postprandial state and stimulated by insulin. The opposite process of glucose synthesis from glycogen (glycogenolysis) is started and stimulated by increased cytosolic Ca^{2+} concentration in the fasting state [2].

Abnormal Ca^{2+} signaling and either insufficient insulin or the lack of glycogen synthesis regulators sensitivity to insulin can lead to whole-body pathologies like obesity and type II diabetes [3].

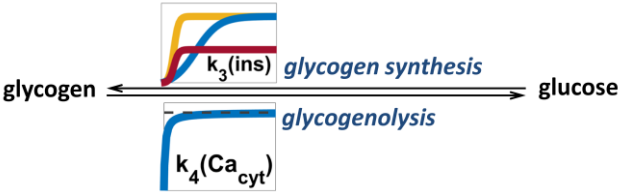

Fig.1. Schematic description of glycogen synthesis regulators sensitivity to insulin in the model (yellow - «norm», blue - «bias», red - «amplitude»)

In the model [4] we show that dysfunctional Ca^{2+} signaling in hepatocytes can lead to improper insulin signaling.

In this work, we extend the model [4] by including a description of hepatocytes' glucose and lipid metabolism processes. Modeling results show that abnormal Ca^{2+} signaling in hepatocytes results in increased plasma glucose level, both intracellular glycerol and TAG concentrations and decreased amount of stored glycogen. In addition, our model results suggest that at normal Ca^{2+} signaling degree of glycogen synthesis regulators sensitivity to insulin (Fig. 1) affects only amounts of stored glycogen.

At dysfunctional Ca^{2+} signaling, decreased glycogen synthesis regulators sensitivity to insulin leads to an even further drop of accumulated glycogen. As for intrahepatocyte glycerol and TAG levels and plasma glucose concentration, the insulin sensitivity affects the range of all three oscillating concentrations, but there is no significant effect on average levels.

Thus, our model allows analyzing the particular role of two different factors as both cytosolic Ca^{2+} and insulin signaling in hepatocytes in the development of glycemic control system pathologies in human organisms.

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RESEARCH OF THE EFFECT OF GAMMA RADIATION AND DOXORUBICIN ON HUMAN TUMOR CELLS

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The leading method of cancer treatment is radiation therapy. There are two main methods of radiation therapy: internal irradiation, in which radiation sources are injected into tissues and external irradiation. Distance learning includes gamma therapy, fast electron therapy, proton and neutron therapy, etc.

In some cases, radiation therapy using photons and electrons may be ineffective due to the fact that radiation cannot be brought to the focus locally enough. At the same time, the problem that has arisen can be overcome by using heavy charged particles: protons, deuterons, alpha particles, fission fragments, heavy ions (carbon), etc. The interaction of heavy charged particles is carried out due to elastic and inelastic collisions with nuclei and electrons, which leads to the excitation or ionization of the target atoms. Proton and carbon beam therapy is currently recognized as the most effective form of radiation therapy for radioresistant and deeply located tumors.

Evaluation of the potential significance of the synergistic interaction of ionizing radiation with chemical preparations in medical radiology remains an urgent problem [1-2].

The aim of the work was to identify the patterns of the combined effect of ionizing radiation and doxorubicin on human tumor cells.

The objects of the study were cell lines: MCF-7 (breast cancer cell line), Hela (cervical cancer), HUH-7 (hepatocarcinoma cells).

Our results show that the synergistic effect manifests itself with an increase in the dose of gamma radiation.

The research revealed the recovery of malignant cells after the combined action of gamma radiation and the drug.

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EFFICACY OF THE MTT-TEST TO DETERMINE CYTOXICITY FOR TUMOR CELL CULTURES OF THREE TYPES

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Cell culture viability studies are performed to determine the response to various agents (drugs, temperature, radiation). The stage of studying the toxicity of the agents is one of the obligatory stages in preclinical studies. According to the recommendations of the European Medicines Agency for the ethical treatment of animals in the testing of drugs - the proportion of preclinical tests will only increase. Therefore, there is an increasing need for high quality evaluation of preclinical test results and effective interpretation of in vitro indications to predict in vivo response on the same or similar cells.

Currently, there are several methods for assessing cell viability, based directly on cell survival or on indirect indications - various biochemical processes, mitotic activity and ect. One of the classic tests for assessing cell viability by biochemical processes is the MTT-test. Initially, this test was developed to assess cytotoxic effects on healthy human cells. But the question arises: how suitable is this method for assessing the viability of various tumor cells.

The objective of this work is to compare the efficacy of using the MTT test to determine the cytotoxicity of doxorubicin and the gamma ray MTT test on tumor cell cultures of MSF-7, HeLa and HUH-7 lines.

Cell cultures of human cervical, breast and hepatocarcinoma tumors cultured under standard conditions at 37°C and 5% CO_2 were studied. Cell cultures were simultaneously exposed to two agents: doxorubicin (concentration 0,004 mg/ml) and gamma radiation. Cells without exposure to the two agents served as a control. To prevent cell reparation after the irradiation procedure, cells were kept at 2-4°C.

The gamma-irradiation was performed on Gamma-irradiation unit GUR-120 at Federal State Budgetary Scientific Institution All-Russian Research Institute of Radiology and Agro-ecology in four doses (1, 2, 4 and 6 Gy) in Eppendorf-type test tubes at the distance from the irradiator - 73 cm, with dose rate 0.9 Gy/min.

The viability of cells was assessed by two methods - the counting of living cells in a Goryaev chamber immediately after exposure and by MTT-test using the standard method for HEK-273 cells line [3].

The use of two criteria for assessment of cell viability gave similar results for HeLa and MSF-7 cell lines, but for HUH-7 cells the MTT-test gave the opposite result in comparison to assessment of survival by cell counting in a Goryaev chamber. The reason for such indicator in HUH-7 line cells is possible with active reparative activity and peculiarities of mitochondria in human hepatocarcinoma. In the future it is planned to evaluate this fact in the field of molecular biology.

Conclusion. MTT-test is suitable for evaluation of viability not only for normal human cells, but also for tumor cells of MSF-7 and HeLa lines.

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FERRIHYDRITE-MEDIATED MONONUCLEAR PHAGOCYTE SYSTEM BLOCKADE FOR IMPROVED TUMOR TARGETING OF NANOMATERIALS

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Nanoparticles (NPs) gained prominence in biomedicine by virtue of diminishing conventional drug side toxicity and bringing advanced technologies for diagnosis, targeted delivery and therapy. However, their potential remains undisclosed due to almost inevitable sequestration by the cells of the mononuclear phagocyte system (MPS), mainly macrophages of liver and spleen, after systemic administration. MPS blockade induced by uptake of high doses of non-functional blocking agents promotes blood circulation of functional NPs and their accumulation in targeted tissues. Despite great efficiency achieved, researchers were concerned about associated toxicity.

Here we demonstrate mononuclear phagocyte system blockade with biocompatible ferrihydrite nanomaterial (Fig. 1), leading to an incredible increase in blood residence time of functional NPs and over twenty-fold rise in delivery efficiency to a tumor. Excellent blockade properties of synthesized ferrihydrite particles were obtained by carboxymethyldextran coating according to the previous research [1].

Ferrihydrite is an endogenous material, ubiquitously used as an iron depot. Ferrihydrite based nanomedicines are used for MRI contrast enhancement and iron deficiency anemia treatment. Consequently, even high doses of the nanomaterial result in little systemic toxicity.

Thus, MPS blockade induced by advanced ferrihydrite-based nanoagents represents a well-tolerated advantageous strategy to boost nanodrug efficiency.

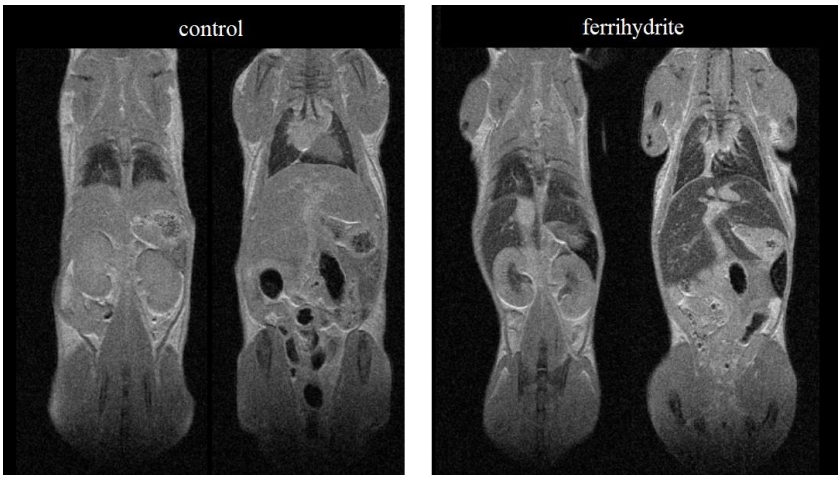

Fig.1. Ferrihydrite-mediated T2-weight contrast of liver, spleen and kidneys (MRI)

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CREATION OF VIRTUAL BIMODAL (WHITE LIGHT AND FLUORESCENT) BLADDER PHANTOMS FOR VERIFYING IMAGE MOSAICING ALGORITHMS

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Fluorescence imaging of organ pathologies is one of the most popular forms of diagnostics during endoscopic examination. However, the limited field of view can make it difficult to interpret images and navigate. Image mosaicing (the process of constructing one high-resolution panoramic image from several images) is a powerful tool for solving this problem. In doing so, it is important to ensure the correct operation of this tool. The aim of this work is to create a virtual phantom for verifying image mosaicing algorithms.

For this we have created a 3D model of the bladder using the free and open source software Blender. Based on the mosaic by Tan-Binh Phan et al. [2], we textured it in two modalities (white and fluorescent light) using real endoscopic data. Then a virtual camera and a light source were placed inside the model and their parameters were set. By setting the trajectories of the virtual camera, we recorded the necessary video sequences. Since Blender has an Application Programming Interface (API), we were able to get the position and orientation of the camera for each frame. This is important for assessing quality, since knowledge of geometry will allow you to build the best metrics.

Thus, we have obtained close to real bimodal video sequences with known geometry on which image mosaic algorithms can be tested (Fig. 1). Also these data are of great practical application in other related fields, for example, when testing algorithms for three-dimensional reconstruction of organs.

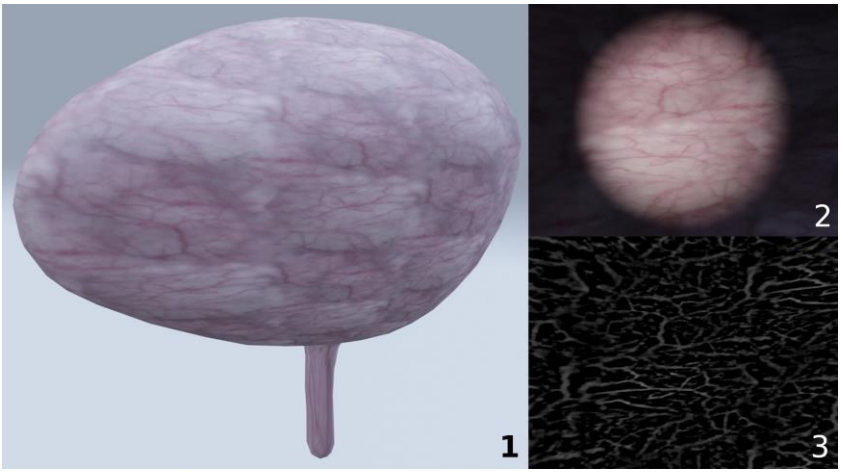

Fig.1. Rendered 3d model of the bladder (1) and frames from the inside of it in white light (2) and fluorescent light (3)

The reported study was funded by RFBR and CNRS, project number 21-58-15005.

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COMBINED EFFECT OF ANTICANCER DRUGS AND SILICON NANOPARTICLES ON BONE MARROW MESENCHYMAL STEM CELLS

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It is known that injecting of mesenchymal stem cells (MSCs) can alleviate the condition of patients even in case of serious diseases [1]. However, the greatest loss of stem cells is associated with cancer. In most countries, including Russia, in terms of mortality rates, they are in second place after cardiovascular diseases and tend to grow [2].

Because anticancer drugs have a destructive effect not only on cancer cells, but also on healthy ones, it is urgent to develop a therapy for their combined action with nanoparticles (NP) as carriers.

We used a bone marrow MSCs of an adult healthy donor. The cells were cultured according to the standard method [3] in plastic Carrel flasks (Sigma, USA) with a bottom area of 25 cm2, into which 2×106 cells were added in 8 ml of RPMI-1640 growth medium (Sigma, USA), containing penicillin (100 U/ml), amphotericin (100 ng/ml), L-glutamine (2 mM), fetal calf serum (20%).

In this work, silicon NP (micro-Psi 5 nm) at a concentration of 0.5 mg/ml were used as drug delivery to cells. The concentrations of doxorubicin and paclitaxel were 0.002 mg/ml and 0.004 mg/ml, respectively, which corresponds to the maximum doses used for treatment.

All experiments were performed in triplicate, each counting about 1500 colonies. The effect of the chemotherapy drug on the cells was assessed by the survival rate.

Fig. 1A shows the survival rate 46% ± 2 under the action of doxorubicin after 2 hours of incubation. Then, the survival rate decreases slightly and after 4 hours and further does not change. With the combined action of the drug with NP, the survival rate continues to decrease and after 7 hours of incubation is 22% ± 2.75. Consequently, NP delivering the drug penetrate into cells, which leads to a decrease in the sur-

vival rate of MSCs. Fig. 1B shows that under the action of paclitaxel, the survival rate in the first hour after exposure is 32% ± 5.15, and with the combined action of the drug and NP it was 3.5% ± 0.75 after 7 hours, which is significantly different when exposed only to the drug. The experiment showed a significant decrease in the survival of MSCs after the combined action of doxorubicin and paclitaxel with NP. It can be concluded that these NP can be used as carriers of chemotherapy drugs into cells.

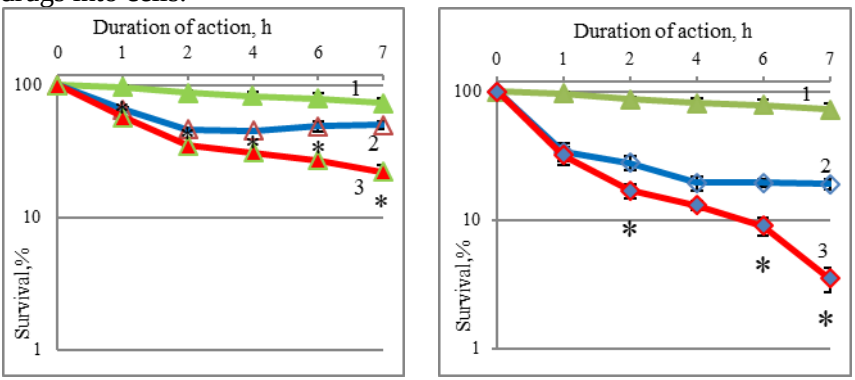

Fig. 1. Changes in cell survival after exposure to doxorubicin and silicon NP (A), paclitaxel and silicon NP (B)
Curve 1 – the effect of NP at a concentration of 0.5 mg/ml; curve 2 – the effect of the drugs at a concentration of 0.002 mg/ml (A) and 0.005 mg/ml (B); curve 3 – combined effect of the drugs and NP.
* – statistically significant differences p <0.05 Cramer-Welch test

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MULTI-ENZYMATIC ACTIVITY OF MALTODEXTRIN-COATED CERIUM DIOXIDE NANOPARTICLES

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Nanocrystalline ceria is prospective material that has found the application both in modern high-tech industries and biomedical branch. Antioxidant potential of cerium oxide nanoparticles is of interest because today much attention is paid to the human protection from the oxidative stress.

Nanocrystalline cerium dioxide is active participant of redox processes [1] due to its structure and unique physicochemical properties. The crystal lattice of nanocrystalline ceria consists of oxygen vacancies and mixed valence states Ce^{3+} and Ce^{4+}. Such structure provides an ability to inactivate free radicals.

Thus, nanocrystalline ceria can perform the functions of different enzymes and non-enzymatic components of the natural antioxidant system. They prevent the damaging effects of reactive oxygen and nitrogen species.

However, along with studies demonstrating CeO_{2-x} ability to protect cells from damage there are studies that have revealed pro-oxidant effects of nanocrystalline ceria [2]. Moreover, some research suggest that nanoparticles are catalytically inert in relation to cells [3]. Thus, there are controversial data in the literature, therefore multi-enzymatic activity of cerium dioxide nanoparticles and laws linking biological activity of nanoparticles with their physical and chemical properties should be studied thoroughly.

The aim of the present paper is to review and analyze the actual data about multi-enzymatic activity of CeO_{2-x} nanoparticles and study this activity using maltodextrin-coated cerium dioxide nanoparticles.

Maltodextrin-coated cerium dioxide nanoparticles are obtained by chemical precipitation [4]. The study of multi-enzymatic activity is carried out by optical spectroscopy.

There are the next results revealed in the present study, namely: cerium dioxide nanoparticles can provide the functions of catalase, peroxidase, oxidase and inactivate hydroxyl radical.

It should be noted that further research is prospective nowadays. The control of physicochemical parameters which cause multi-enzymatic activity will make the creation of targeted remedies possible. The development of this topic will allow us to synthetize nanomaterials with specified characteristics for specific medical applications. It is especially important from the scaling of the nanoparticles production processes point of view.

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MODEL QUANTITATIVE CHARACTERISTICS OF STRUCTURAL ELEMENTS OF "LINES" IN THE TASKS OF AUTOMATING THE DIAGNOSIS OF MELANOMA

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Melanoma is considered one of the most malignant skin neoplasms requiring early diagnosis. There is no universal diagnostic algorithm for this disease; therefore, various instrumental diagnostic methods are used [1–3], for example, light dermoscopy, non-invasive epidermal genomic detection and confocal scanning laser microscopy, etc.

The main task of research work is to help doctors diagnose skin neoplasms (benign or malignant).

The main tasks that solve for this: selection of "line" and "network" elements on the neoplasm, calculation of quantitative characteristics of "lines" and "networks", creation of a classifier based on the obtained characteristics for the classification of a neoplasm.

For detection lines or networks use binarization with a single threshold, adaptive binarization, bitwise operations with images, morphological operations with images (opening, closing) and the Zhang-Suen skeletonization algorithm.

After highlighting lines or networks calculate their characteristics. Such as length, width, RGB components.

To classify the neoplasm based on the obtained characteristics of the lines and the network used a naive Bayesian classifier. For the classification used each characteristic separately.

Classification accuracy results: length – 65%, width – 62%, R – 65%, G – 53%, B – 46%.

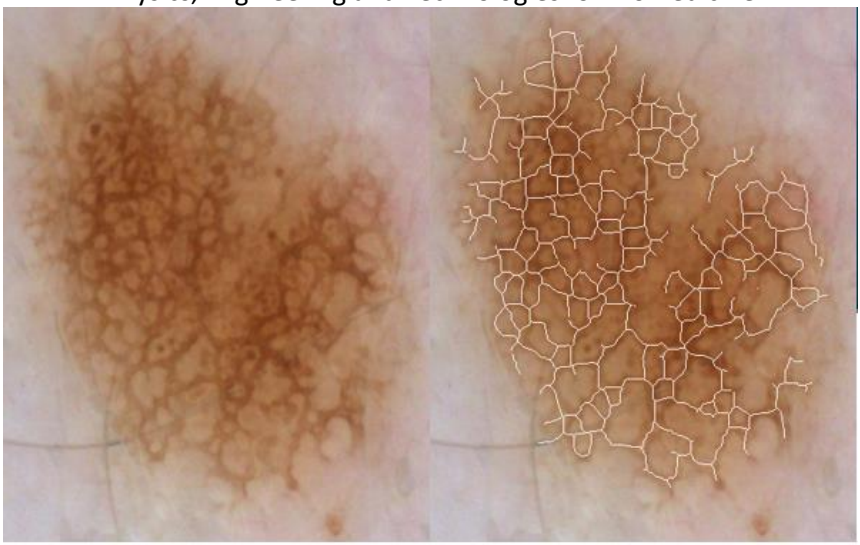

Fig.1. Line detection result. Left: original image. Right: processed by the algorithm

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METHOD FOR RECOGNIZING LEUKOCYTES ON IMAGES OF BONE MARROW PREPARATIONS IN CONDITIONS OF MULTIPLE CONTACT OF CELLS

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A problem of classification of leukocytes on images of bone marrow smears for automated diagnosis of diseases of the hematopoietic system is reviewed. A method for solving the problem of classifying contiguous leukocytes on images of bone marrow smears is proposed. Bone marrow examination is necessary if acute leukemia is suspected. The subjectivity and complexity of the study, as well as the time spent on it by a specialist, make it relevant to develop methods for automating the processes of blood and bone marrow analysis [1-4].

The experimental research methodology includes the following stages: collection and preparation of initial data, extraction of leukocyte nuclei from images, training of the classifier and its application. 570 microscopic images of bone marrow cells were used as initial data. The training sample consisting of 628 lymphoblasts, 401 granulocytes, 507 lymphocytes and 147 monocytes was taken from the knowledge base of the Department of Computer Medical Systems of the National Research Nuclear University MEPhI.

The proposed image processing model includes the following main stages: preprocessing, segmentation, feature detection and cell classification. Preprocessing includes noise filtering, converting a color image to a halftone by selecting the G component of the RGB model. The segmentation process is clearly visualized on Figure 1.

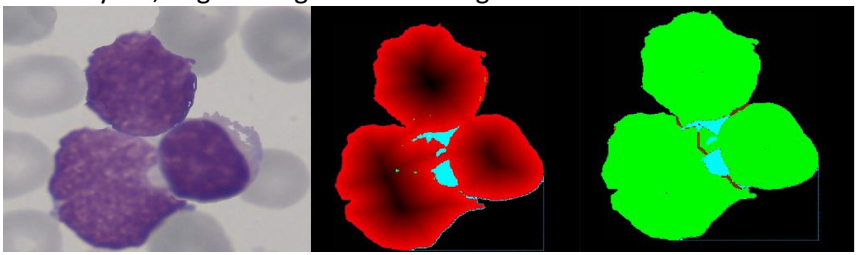

Fig.1. Illustration of the segmentation process of touching leukocytes

After separation, signs are counted for all found leukocytes. The following features are used: area, perimeter, nuclear-cytoplasmic ratio, shape coefficient, circle filling coefficient, cytoplasm brightness, core brightness. Classification is performed based on the K-means clustering method. The following modification is proposed: at the beginning, the classifier is pre-trained by calculating the average value of cell features for the training sample.

The accuracy of recognition of lymphoblasts, granulocytes, monocytes, lymphocytes is 79-88%, depending on the type. The considered approach can be effectively applied in the development of medical decision support systems in hematology.

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SUBSTRATE-DEPENDENT OPTICAL PROPERTIES OF ORGANOMETAL PEROVSKITE NANOCRYSTALS

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Organometal perovskite (OMP) nanocrystals (NCs) attract a great interest because of tunable photoluminescence (PL) with a high quantum yield, that makes them promising for optoelectronics, light emitters and other applications [1,2].

The aim of our work was to investigate PL properties of OMP NCs deposited on different substrates. The permittivity of water-rich tissues differs dramatically from the open air. Moreover, various shells can be used to passivate hazardous or unstable particles [2]. So, the effect of surrounding material must be well-known and predictable.

In our work we investigated PL of methylammonium lead bromide (MALB) perovskite NCs with sizes about 100 nn. MALB NCs suspension was deposited as a thin layer onto substrates with different permittivity, i.e. fused quartz and monocrystalline silicon (c-Si). PL was excited at 365 nm (light emitting diode). The obtained PL spectra are shown in Fig.1.

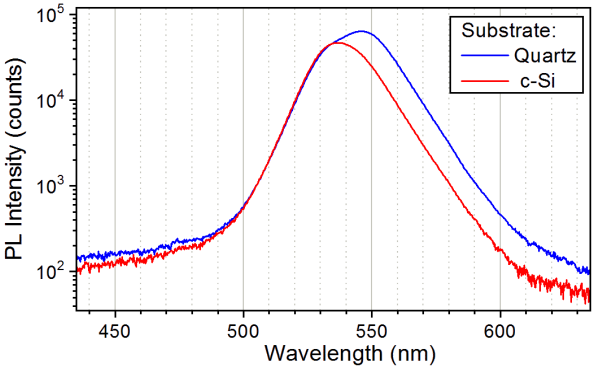

Fig.1. PL spectra of MALB NCs on different substrates (excitation at 365 nm)

Increasing the substrate permittivity (11.7 for c-Si against 4.3 for quartz) leads to the PL maximum shift towards shorter wavelengths. The observed shift was about 10 nm. Since the PL mechanism in perovskites involves Wannier – Mott excitons [3], the observed effect can be explained by localization of excitons. The more the permittivity of surrounding substance the less electric field penetrates into this substance from a nanocrystal. So, the exciton radius is more expanded and the exciton binding energy is lower for the c-Si substrate.

Thus, this work shows that the PL properties of OMP NCs depend on substrate permittivity (besides temperature and NCs size) and the application of such NCs requires taking it into account.

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STUDY OF LOCAL ELECTROMAGNETIC FIELD ENHANCEMENT BY IRON OXIDE NANOPARTICLES

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This work is dedicated to the study of iron oxide nanoparticles (FeO-NPs) coated with photosensitizers (PS) in the aspect of their application for precision phototherapy of oncological diseases prone to metastasis.

In recent years, there has been a growing interest in the development of phototherapy methods using nanostructures to increase the selectivity and effectiveness of treatment. A large number of studies are devoted to FeO-NPs [1]. Data on the immunosensitizing antitumor effects of FeO-NPs on the growth of early forms of breast cancer and metastases of lung cancer have been published [2]. In addition, for phototherapy, FeO NPs can be functionalized using PS, while an increase in the generation of singlet oxygen and an increase in the selectivity of delivery in vitro and in vivo are observed [3].

In this work, we studied FeO NPs coated with zinc and aluminum phthalocyanines. Using the finite difference method, mathematical modeling of the amplification of the electromagnetic field and the subsequent electrical breakdown between FeO NPs of different sizes, caused by exciting laser radiation, depending on the intensity and wavelength of laser radiation, was carried out. The simulation results were compared with experimental data. Intracellular localization of FeO-NPs in THP-1 human monocyte cell culture was studied using laser scanning microscopy; phototoxicity depending on wavelength (CW lasers 488 nm, 561 nm, 633 nm and pulsed femtosecond laser in the range of 700 - 900 nm), laser intensity and radiation dose.

The results of theoretical modeling made it possible to reveal the optimal sizes of FeO-NPs and the distance between them to ensure local

amplification of the electromagnetic field by several orders of magnitude. It has been shown that in order to obtain the maximum field amplification in the red spectral range, it is most promising to use dimers consisting of FeO-NPs that differ significantly in size (for example, 150 nm and 50 nm).

In vitro, the photoinduced phenomenon of "sparking" was demonstrated for FeO-NPs coated with phthalocyanines, under irradiation with red laser light, which leads to immediate cell death. The observed effect significantly enhances the therapeutic effect of phototherapy in vivo [4].

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ULTRA-SHORT PET/CT ACQUISITIONS FOR DIFFERENTIAL DIAGNOSIS OF GLIAL BRAIN TUMORS

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The radiopharmaceutical 11C-methionine in PET examination of the brain tumors provides high contrast imaging due to the fact of increased accumulation in lesion in comparison to the intact normal tissue, which makes it possible to clearly identify the tumor boundaries. This elevated accumulation is based on increased protein synthesis and active transmembrane transport.

Typical MET PET/CT study time of 20 minutes (10 minutes for uptake time and 10 minutes of scanning) was compared with the reduced acquisition times (2, 4 and 10 minutes after the administration of the radiotracer) to evaluate the possibility to reduce scan time without compromising the examination quality. Extra parameters of the first minute of the study such as the tumor-to-normal-ratio at 1 minute (T/N_1min), as well as the T/N at the moment of the peak passing were introduced.

Data were collected from 89 patients to develop short scanning protocol. Scans of 2 minutes, 4 minutes and 10 minutes were simulated based on the data acquisition, with the datasets having fewer frames compared to the 20-minute study (9, 14 and 22, respectively, compared to 26 frames). Patients were divided into groups based on tumor malignancy and the duration of the simulated study. Eventually, there were 12 groups of patients. Since the data were normally distributed Student's t-test was used to analyze the statistical difference between the modeled datasets.

T/N of simulated accelerated protocols and T/N of standard research protocols are statistically indistinguishable ($p > 0.05$). As a result of this, accelerated brain scan protocol can be used in clinical research

This technique allows reducing the study time for one patient to 4 or 10 minutes and introduce additional parameters of the first minute of the study, such as T/N_1min, as well as T/N at the time of passing the peak on the radiopharmaceutical accumulation graph for differential diagnosis.

METHOD FOR DETERMINING THE EDGE OF GLIOBLASTOMA TUMORS BASED ON AUTOMATIC CLASSIFICATION OF THE TISSUE RAMAN SPECTRA

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The main difficulties of neurosurgery of intracranial tumors are associated with the complexity of demarcation of their boundaries due to the peculiarities of their growth. Infiltration of tumor cells into healthy tissue makes radical resection impossible without significant neurological deficits for the patient. In recent years, many other methods have been investigated for determining tumor margins, including Raman spectroscopy. It allows detecting differences in the composition of the studied tissues in the absence of a fluorescent marker.

The Raman spectra of glioblastoma tissue samples were recorded ex vivo under 785 nm laser excitation with a fiber-optic probe for delivering laser radiation and Raman signal. Subsequent verification of samples was performed using pathomorphological methods.

A technique for registration and processing of Raman spectra using Principal Component Analysis with subsequent classification using Support Vector Machine method has been developed to determine the boundaries of the glioblastoma tumor tissue. Based on the measured Raman spectra, this technique made it possible to correctly distinguish between malignant and normal tissue with up to 88% accuracy.

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THE EFFECT OF 5-AMINOLEVULINIC ACID ON THE METABOLISM OF CANCER AND IMMUNOCOMPETENT CELLS

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There is a growing interest in the immunostimulating properties of photodynamic therapy (PDT). Here, we investigated the effect of the well-known photosensitizer protoporphyrin IX (PpIX), produced from 5-aminolevulinic acid (5-ALA), on the metabolism of tumor cells and activated macrophages. PpIX is produced in mitochondria in a cascade of heme synthesis reactions; the accumulation of PpIX in cells depends on their metabolic activity, which can lead to the selectivity of PpIX accumulation within the cell population with different severity of dysfunctions.

PpIX accumulation was estimated using confocal microscopy. The visualization of the cells metabolic state was performed by the metabolic cofactors NADH and FAD fluorescence using fluorescence lifetime imaging microscopy (FLIM). There were demonstrated significant differences in PpIX accumulation between non-activated monocytes and activated macrophages. It was found that 5-ALA induced PpIX accumulation in macrophages is sensitive to their polarization. The intensity of the PpIX was higher in LPS-activated cells. Due to incubation with 5-ALA, the cells changed the ratio of bound and free NADH.

Low-dose PDT can change macrophages polarization. A high dose of PDT led to the repolarization of all macrophages to the M2 type. For low-dose (5 J/cm^2) PDT, M0 macrophages turned to M1 phenotype. In other cases, the M2 type predominated slightly. For M1 macrophages, the apoptotic type of cell death prevails during PDT treatment with a dose of 5 J/cm^2. For a dose of 50 J/cm^2, necrosis predominates in all macrophage types.

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TRIGLYCERIDE DIFFUSION IN ONE- AND TWO-COMPONENT MEDIUM: MOLECULAR DYNAMICS SIMULATION

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Triglycerides are the main form of lipid storage in a living cell. Lipid droplets are formed inside the cell to store triglycerides. These cellular organelles regulate the storage and hydrolysis of triglycerides. Lipid droplets reach the most significant size in white adipocyte cells [1].

The size of a lipid droplet is not constant. Depending on a diet, the lipid composition of the contents of the droplet also varies. With a sharp transition from one long-term diet to another with a different lipid composition, the contents of a lipid droplet may be considered a two-component medium in which mixing is possible due to diffusion processes.

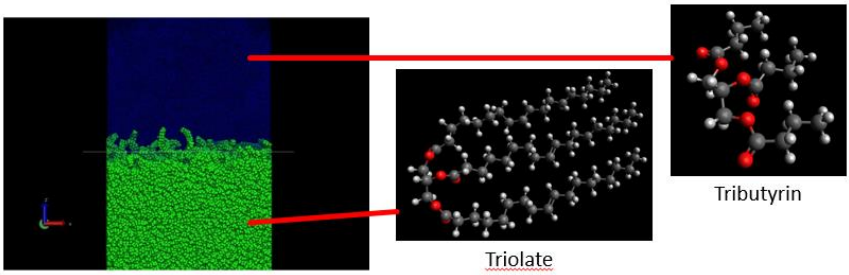

Fig.1. Modeling scene for two-component medium

In this work, we study several different triglyceride molecules using the methods of full-atomic molecular dynamics simulation [2]. Densities and diffusion coefficients of triglyceride molecules were obtained for one-component media (results correlate with available experimental da-

ta [3]), and radial distribution functions were constructed to determine the aggregate state of the substance.

In addition, the structure, physical properties, and dynamics of the transition layer between two types of triglycerides were investigated (see Fig. 1). The simulation results allow us to estimate the coefficient of mutual diffusion.

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PROSPECTS FOR THE STUDY OF TRANSGENERATIONAL EFFECTS IN *DAPHNIA MAGNA* IRRADIATED AT VARIOUS STAGES OF EMBRYOGENESIS

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Currently, transgenerational effects are actively studied in human radiobiology and epidemiology. Preliminary laboratory tests on alternative objects are an important part of radiobiological research in humans. *Daphnia magna* represent a convenient experimental model that allows to analyze many aspects of long-term exposure to ionizing radiation, including transgenerational effects. These freshwater crustaceans are distinguished by relatively short lifespans, embryonic and postembryonic periods. As a rule, the relevant studies are carried out in the postembryonic period of animal development. At the same time, the identification of vulnerable stages of embryogenesis will provide the most complete understanding of the effects of the stress factor.

The purpose of this work is to determine the potentially most sensitive stages of Daphnia embryogenesis for subsequent study of the radiation toxic effect.

The late embryogenesis of crustaceans is assumed to proceed according to the general scheme and includes 4 stages [1]: 1) the stage of development of the brain and thoracic department 2) the formation of the trunk limbs 3) the formation of the eye capsule and the registration of the first heartbeats 4) the stage of functional integration (the first registration of coordinated movements of the oral apparatus and trunk limbs) 4) the exit of embryos from the brood chamber. ы

The publication [2] shows that the embryogenesis of *Daphnia pulex* is plastic, and the duration of the stage correlates with the development of certain traits in offspring. The nature of the embryogenesis course may reflect the features of further ontogenesis of Daphnia. This fact,

according to the authors, can be applied in standard toxicity tests for Daphnia. The advantage will be the opportunity to study a large number of individuals in a relatively short time.

D. magna females demonstrate a decrease in fertility in the first generation after exposure to a low-frequency electromagnetic field (EMF) directly at the stage of embryogenesis. [3]. However, it is emphasized that follow-up monitoring of irradiated individuals and their offspring is necessary.

Thus, Crustaceans are organisms with a well-studied cycle of embryogenesis, in particular, the periods of formation of certain organs. It can be assumed that these periods are sensitive to the action of ionizing radiation and critical for the development of viable individuals. The relationship between such exposure and potential changes in the ontogenesis of individuals developed from an irradiated embryo may become an important new parameter for studying the dynamics of long-term effects of irradiation.

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NUMERICAL AND EXPERIMENTAL INVESTIGATION OF HEAT PROPAGATION PROCESSES IN BIOLOGICAL TISSUES DURING PHOTOHYPERTHERMIA WITH THE USE OF TITANIUM NITRIDE NANOPARTICLES

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The problem of cancer treatment is very acute nowadays. Existing methods of treatment, such as chemo- and radiation therapy, have a number of serious side effects on the human body, significantly reducing the quality of life of patients [1]. One of the alternative methods of cancer treatment is local photohyperthermy of cancer cells using nanoparticles. As part of this study, titanium nitride nanoparticles with high biocompatibility with the human body were selected [2].

To study the process of heat propagation during photohyperthermy of the cancer area, a numerical and physical model of the tissue is being developed in order to select and determine the optimal parameters of irradiation and heating to achieve the best effectiveness of therapy.

The current results of work in this direction are presented in this report.

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SILICON AND IRON COMPOSITE AS NANOMATERIAL FOR PHOTOTHERMAL TREATMENT OF CANCER

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Silicon and iron composite has been synthesized by femto-second laser ablation of the target, prepared of silicon and α-iron silicide mixture, in acetone. Scanning Electron Microscopy showed that the composite consisted of spherical nanoparticles with diameter range from 20 to 250 nm. Raman spectroscopy revealed the presence of crystalline silicon in the composite. Synthesized composite demonstrated low transmittance, efficient photon conversion (~ 17.0 %) and excellent photostability. We think that the composite may be used as nanomaterial for photothermal treatment of cancer.

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APPLICATION OF RAMAN MICROSPECTROMETRY TO STUUDY LOCAL BLOOD OXYGENATION AND REDOX STATE OF THE MITOCHONDRIAL RESPIRATORY CHAIN

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Raman spectroscopy (RS) is a non-destructive and sensitive method for the investigation of molecular vibrational modes and it found wide applications in many fields, including biology and medicine. This method allows to study changes in conformation and function of biomacromolecules inside cells *in vitro* and *in vivo*. Previously Raman spectroscopy was extensively used to study isolated heme-containing molecules (e.g. hemoglobin (Hb), myoglobin and cytochromes). Raman spectra are sensitive to the degree of blood oxygenation, which makes it possible to estimate local blood oxygenation in the brain in real time.

In this study, the RS-based technique was developed for the simultaneous investigations of the brain cell properties and of the degree of blood oxygenation in the vessels of the cerebral cortex in anesthetized mice. 2-3 months before RS experiments a craniotomy surgery was performed on a mouse with the removal of a part of the skull above the somatosensory cortex with the installation of a transparent glass window that protects the exposed brain tissue and allows the registration of Raman spectra. Experiments were performed with confocal Raman microspectrometer InVia Qontor (Renishaw, UK) with 532 nm laser.

Raman spectra of arterioles and venules represent peaks corresponding to vibrations of bonds in heme molecules of hemoglobin (Hb). Positions of peaks depend on the Hb oxygenation and differ for oxy-and deoxyHb [1]. Thus, Raman spectra of brain vessels can be used to estimate the degree of local blood oxygenation. Raman spectra recorded from neurons or glial cells demonstrate peaks with the positions of the 750,

1126, and 1585 cm^{-1}, corresponding to the vibrations of heme bonds in the reduced cytochromes C and B-types in respiratory chain of mitochondria. Peaks with the positions at 1440 and 1660 cm^{-1} correspond to vibrations of bonds in lipids and proteins, respectively. These peaks can be used to assess the redox state of mitochondrial cytochromes and the protein-lipid composition of the cytoplasm of cells (Fig.1). Recording of Raman spectra from astrocyte end-feet near blood vessel allows simultaneous estimation of mitochondria redox state in astrocyte and blood oxygenation in the adjacent vessel (Fig.1).

Thus, we have developed RS-based methodological approach for the non-invasive registration of Raman spectra from cells and blood vessels of the mouse brain *in vivo*, which can be used to study the interaction between brain cells (neurons and astrocytes) and blood vessels.

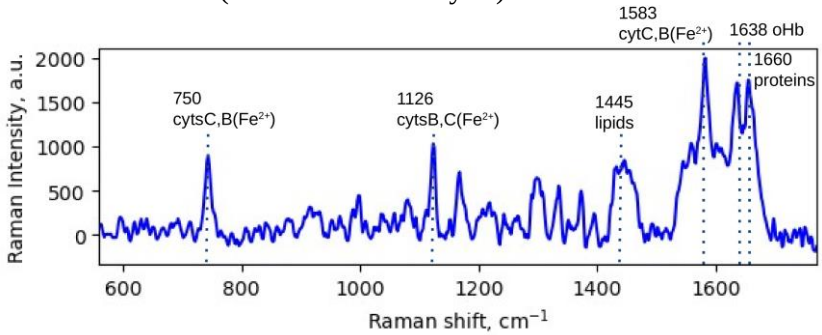

Fig.1. Raman spectrum of an astrocyte and adjacent arteriole in the somatosensory cortex of anesthetized mouse. Peak maxima positions and their relation to certain molecules are marked above the peaks

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DELIVERY OF NANOPARTICLES INTO THE CELL USING ISOLATED MITOCHONDRIA

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Nanoparticles are one of the promising means of therapy and diagnosis of various diseases.

One of the problems hindering the introduction of nanomaterials into medical practice is the lack of tools for their delivery into cells. We developed a new approach of transporting nanoparticles inside cells using isolated mitochondria. The choice of mitochondria as an instrument for the delivery was due to their low immunotoxicity in vivo and natural presence in the bloodstream of mammals.

Mitochondria were isolated from mouse liver by tissue homogenization and subsequent organelle separation by centrifugation. All manipulations were performed at 4 ° C to avoid activation of damaging phospholipases and proteases. The integrity of the organelles after the isolation was confirmed by scanning electron microscope.

Then we tested the viability of isolated mitochondria by measuring activity of membrane respiratory chains. Mitochondria were stained with dye Rhodamine 123, which is sensitive to the membrane potential. A decrease in relative fluorescence was observed with the addition of proton carriers (ascorbic, glutamic, succinic, malic acids in the presence of adenosine diphosphate ADP) and an increase with the addition of disconnectors and inhibitors of membrane complexes (FCCP, rotenone) due to changes in the membrane potential. The above indicates the viability of isolated mitochondria and the absence of their significant damage during isolation.

Also, the possibility of delivering nanoparticles on the surface of mitochondria to cells in vitro was tested. The mitochondria were dyed with fluorescent nanoparticles, the excess of which was removed by centrifugation, and incubated with mouse epithelium cells and human tumor cells. Confocal microscopy in the dynamic showed the active penetration of the mitochondrial complex with nanoparticles into the cells.

Thus, it has been shown that coating isolated mitochondria with nanoparticles is a novel tool for delivering nanomaterials inside cells. The presented method makes it possible to deliver the drug intracellularly, which significantly reduces the drug load on the body and the probability of side effects of the treatment. The use of nanoparticles modified by anti-tumor antibodies potentially can improve therapy and diagnostics of malignant tumors.

The work was supported by the grant of the Russian Science Foundation № 21-74-30016.

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INVESTIGATION OF THE OPTICAL PROPERTIES OF PHEOPHORBIDE A AGGREGATES IN BIOCOMPATIBLE MEDIA

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For the current period, many studies have been devoted to sonodynamic therapy (SDT) of oncology diseases [1]. The essence of this method is that the effect of therapeutic ultrasound (1-3 MHz, 0.1-4 W/cm^2) in combination with a classical photosensitizer (PS) leads to the degradation of cancer cells by activating several mechanisms.

The first mechanism is directly related to the cavitation bubbles generated by ultrasound, which are capable of creating mechanical damage to cells by a shock wave as a result of their collapse. At the same time, the use of nanoparticles and molecular aggregates in combination with ultrasound can lead to an increase in sonochemical and sonomechanical reactions. The rough surface of nanoparticles or molecular aggregates leads to an increase in the number of cavitation bubbles in the solution/cells. Thus, activated by ultrasound, nanoparticles or aggregates of molecules can initiate inertial cavitation inside or near cells, causing cytotoxic effects [2]. The second mechanism is associated with the activation of molecules by cavitation effect named sonoluminescence (SL). Photoexcitation of molecules by SL leads to the generation of reactive oxygen species (ROS) and subsequent apoptosis or necrosis of cancer tumors, similar to PDT [3].

In this work, aggregates of pheophorbide a (Pha) molecules in biocompatible solvents were created and their optical properties were investigated.

It should be noted that the formed aggregates can be both luminescent and non-luminescent. Non-luminescent aggregates are more likely to be unable to generate ROS; accordingly, aggregates of this type can only be used to enhance the cavitation effect. Luminescent aggregates,

with high efficiency of reaching the triplet state, are capable to generation ROS but with lower efficiency compared to monomers of Pha molecules [4]. In this case, aggregates of Pha molecules can generate ROS and enhance the cavitation effect. So, these aggregates of molecules combine the properties of a sensitizer necessary for the effective operation of both mechanisms for SDT.

In this work, the optical properties of aggregates of molecules - photosensitizers Pha. The quantum yield of singlet oxygen generation was estimated for aggregate of Pha. Analysis of the obtained aggregates showed that they can be used as a sensitizer for the effective operation of such mechanisms of sonodynamic therapy as cavitation centers for enhancing sonomechanical reactions and as a source of ROS generation.

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A PRIVATE PROBLEM OF TREATMENT OF NOSOCOMIAL INFECTIONS CAUSED BY ANTIBIOTICORESISTENT STRAINS

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In the treatment of purulent-inflammatory infections, an antibiotic with a local anesthetic is often used [1].

Aim. To study in vitro the effect of a combination of ceftriaxone and lidocaine in culture of microorganisms.

Materials and equipment. The in vitro study used nosocomial strains of S. aureus and E. coli. To diagnose the effect of the development of antibiotic resistance, the disc-diffusion method was used. The effect of the following drugs has been studied: ceftriaxone is a parenteral cephalosporin of the third generation, which has high activity against gram-positive and gram-negative bacteria [2]. Lidocaine is a short-acting local anesthetic of the amide type. In therapy, a 1% solution is used [3].

Results. in vitro in the culture of pathogenic staphylococci and Escherichia coli, ceftriaxone is effective and has a pronounced antibacterial effect in 90% of cases. Lidocaine in vitro in bacterial culture did not exhibit antibacterial properties.

With the combination of ceftriaxone and lidocaine preparations in vitro in the culture of S. aureus bacteria in 40% of the samples, the growth inhibition zone falls to the border of low effective. This indicates a pronounced decrease in the sensitivity of the culture to the antibiotic.

It should be noted that E. coli did not change antibiotic sensitivity against the background of the combination of drugs.

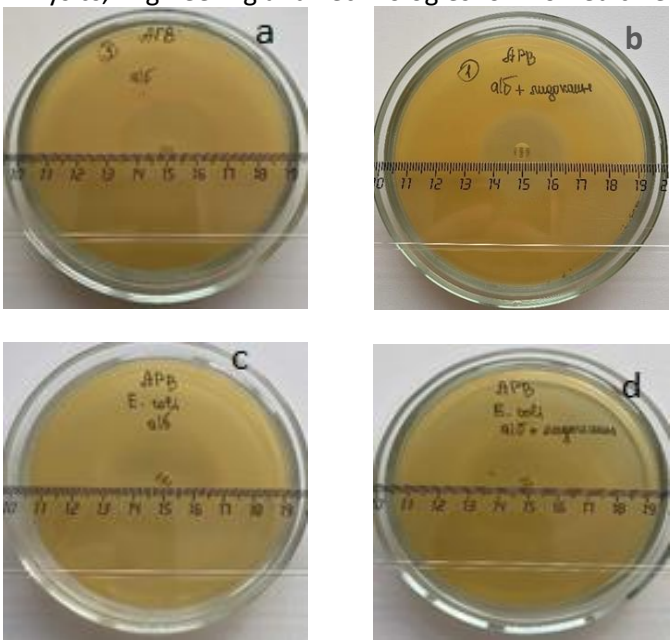

Fig.1. Disk-diffusion method ceftriaxone (a), ceftriaxone and lidocaine S. aureus (b), ceftriaxone (c), ceftriaxone and lidocaine (d) E. coli

Conclusions. The combined use of ceftriaxone with lidocaine may lead to a decrease in its antibacterial efficacy in vivo in the treatment of nosocomial infections.

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LASER SYNTHESIS OF STABLE SIZE-TUNABLE BI BASED NANOCOMPLEXES AND THEIR FUNCTIONALIZATION FOR ADVANCED RADIOTHERAPY

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Radiation nanomedicine is an emerging field, which utilizes nanoformulations of high-Z elements to increase their local concentration at targeted sites to improve therapeutic outcome and to reduce radiation dosage. This field lacks methods for controlled fabrication of biocompatible, non-toxic nano-agents with low polydispersity and high colloidal stability, which are required for efficient targeted cancer treatment. Here, we present application of methods of femtosecond (fs) laser ablation in water and organic solvents, which we developed in our previous works [1,2], to fabricate stable aqueous colloidal solutions of ultrapure elemental Bi nanoparticles (NPs) and their characterization. We demonstrate that fs laser ablation of Bi target leads to the formation of spherical elemental Bi NPs with 25 nm mean size and wide size-dispersion. The NPs prepared in water undergo fast conversion into 400-500 nm flake-like nanosheets, while the NPs prepared in acetone demonstrate high colloidal stability. We elaborate a technique for control mean size and width of size distribution for spherical Bi NPs by methods of fs laser fragmentation. Stable aqueous solution of Bi NPs suitable for biomedical applications can be obtained by coating with Pluronic® F-127. We show that surface modification of Bi NPs increases its colloidal stability in phosphate buffer saline (PBS) solution by more than 6 folds. Exempt of any toxic synthetic by-products, laser-ablated Bi NPs present a novel appealing nanoplatform for combination image-guided photo- and radiotherapies.

We found that the presence of water played a decisive role in the final morphology and composition of Bi NPs: even the addition of 1% v/v of water to LAA Bi NPs resulted in a change of NPs shape from spherical to flake-like nanosheets. The morphological alterations were accompanied by a change in chemical composition of NPs: elemental Bi turned into Bi subcarbonates $(BiO)_2CO_3$ and $(BiO)_4CO_3(OH)_2$ [3]. Typical STEM images and size distributions of Bi NPs obtained by laser ablation in acetone and water are shown in Figure 1.

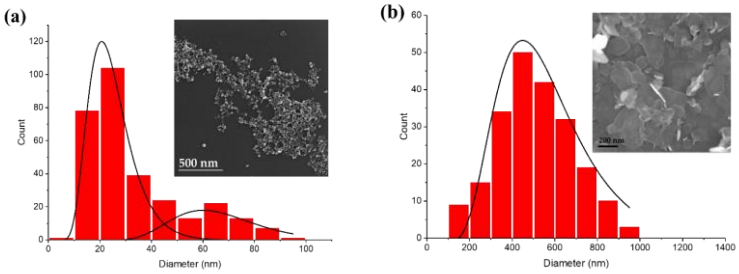

Fig. 1. Size distributions with typical scanning transmission electron microscopy (STEM) images of Bi NPs after fs laser ablation in (a) acetone and (b) water

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OPTIMIZING THE ELECTRON TRANSPORT IN QUANTUM DOT LIGHT-EMITTING DIODES

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Quantum dots (QD) are promising materials for future light emission diodes (LEDs, QDLEDs). In comparison with organic materials, their thermal and photo- stability allow achieving greater device brightness due to higher current density. However, the imbalance in the carrier injection/transport rates is one of the weakest points of QDLEDs [1], because excess charges accumulated in the emitting layer quench QDLED emission due to various non-radiative processes. The imbalance of charge carriers in LEDs is associated with the presence of high potential barrier for hole injection into the QD layer, accompanied by the greater mobility of negative charges in the electron transport layer. To solve this problem, an electron-blocking layer (EBL, eg. made of PMMA [2]) can be introduced, which makes it possible to regulate the flow of electrons into the emitting layer.

Here, we have investigated the dependence of the luminosity and current efficiency of a multilayer QDLED with ITO/PEDOT:PSS/poly-TPD/PVK/QDs/PMMA/ZnO/Al structure (Fig. 1) on the thickness of its EBL. To do this, a series of devices was fabricated with PMMA layer thickness ranging from 0.13 to 3.1 nm (Table 1). By tuning the latter value, we fabricated a device with brightness exceeding the one of the control device without EBL by four times, increased current efficiency by almost an order of magnitude and turn-on voltage lowered by about 1

V. Therefore, it can be concluded that tuning the EBL of a QDLED device is a profitable strategy to improve charge carrier balance and thereby achieve efficient light emission.

Table 1. Summary of the performance parameters of the fabricated QDLED devices with and without a PMMA layer

PMMA layer thickness, nm	3.1	2	1	0.5	0.25	0.13	w/o PMMA
Turn-on voltage, V	3.6	2,9	2.5	2.3	2.1	2.1	3.3
Maximum current efficiency, Cd/A	0.05	0.57	1.81	0.92	1.0	1.05	0.98
Luminance, Cd/m^2	33	635	9093	8146	9969	18671	4472

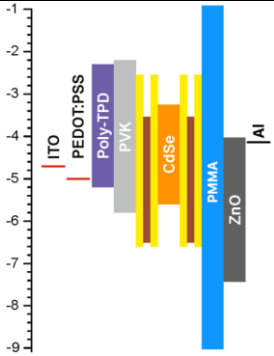

Fig.1. Flat-band energy level diagram of the fabricated QDLED device

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DYSFUNCTION OF FUNCTIONAL CONNECTIVITY BETWEEN DEFAULT MODE NETWORK AND FUSIFORM GYRUS IN PATIENTS WITH MCI. RSFMRI STUDY

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Introduction: Mild cognitive impairment (MCI) is the stage between the expected cognitive decline of normal aging and the more serious decline of dementia. It's characterized by problems with memory, language, thinking or judgment [1]. It is extremely important to study not only structural but functional changes to allow the early detection of mild cognitive impairment and Alzheimer's disease.

Materials and methods: We studied two groups of patients. 17 patients with MCI (mean age – 68.6 years) were studied. The control group consisted of 14 healthy volunteers (mean age - 65.7 years). All MRI studies were performed on a Philips Achieva dStream 3.0T scanner. A 5 min rsfMRI gradient-echo echo planar imaging (EPI) sequence was acquired (TR=3000 ms, echo time [TE] = 35 ms, 100 fMRI scans). fMRI data were processed using functional connectivity toolbox CONN.

Results: Intergroup seed-based correlation ROI analysis revealed statistically significant (p=0,028, FDR) decrease in functional correlations between Default Mode Network Hubs (MPFC, PCC, LP l, LP r) and Temporal Fusiform Gyrus (anterior division) in group of patients with MCI.

Discussion: It is known that the fusiform gyrus is an important brain area involved in facial cognition; altered connectivity of FG to some other regions may lead to a deficit in visual cognition [2]. Other authors [3] reported that FG plays critically important role in core behavioral profile of semantic dementia.

Given the important role of DMN structures in the brain cognitive functions, our results of changes in the neural connection between DMN regions and fusiform gyrus may provide insight into the understanding

of cognitive decline in patients with MCI. We are confident that further research in this area will demonstrate whether analysis of the functional integrity of DMN can serve as a biomarker for monitoring the recovery of patients with MCI.

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EFFECTS OF 3-HYDROXYPYRIDINE FUMARATE ON HELA CELLS

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The use of chemotherapy to treat cancer began at the start of the 20th century with attempts to narrow the universe of chemicals that might affect the disease by developing methods to screen chemicals using transplantable tumors in rodents [1]. Despite the rather long history of the use of chemotherapeutic drugs in oncological practice, the search for new compounds with antitumor activity continues. The aim of this search is to improve the effectiveness of therapy and reduce the incidence of side effects [2].

The aim of this work is to study the effect of 3-hydroxypyridine fumarate on HeLa cancer cells.

Test objects - HeLa cancer cells. The investigated drug is 3-hydroxypyridine fumarate.

The cells are cultured according to a standard technique until reaching 60% -80% of the confluent layer.

In the group with drugs to the growing medium, add a solution of the drug at the calculated concentration and continue cultivation for another 1 day.

On the day of the experiment, the cells are removed from the culture flasks using a trypsin solution and placed in ependorfs (2 ml) at a predetermined concentration with the culture medium. The drug was added at a concentration of 0.01 mg / ml. Irradiation is carried out in doses of 1 Gy, 2 Gy, 4 Gy, 6 Gy (Power 0.9 Gy / min).

Cells were counted using a Goryaev chamber. The results were compared with controls. A cell culture irradiated without the drug in the same doses was used as a control.

As a result, it was found that the doubling time under the action of the drug (3-hydroxypyridine fumarate) increased significantly and amounted to 48 hours.

With irradiation at a dose of 1 Gy, the doubling time increased by 6 hours and amounted to 12 hours. Irradiation at a dose of 2 Gy increased the doubling time to 24 hours. With irradiation at a dose of 4 and 6 Gy, the doubling time increased to 48 hours.

With the combined action of the drug and irradiation at doses of 1, 2, 4, and 6 Gy, the doubling time increased to 20.5; 28.8; 48 and 20.5 hours, respectively.

Thus, 3-hydroxypyridine fumarate significantly increases the doubling time of HeLa cancer cells.

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SOLID-STATE RARE-EARTH LASERS IN BIOMEDICAL APPLICATIONS

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The development of laser technology has now reached such a level that with its help it is possible to solve many technical problems. Laser technology is applicable to objects made of a wide variety of materials in various states of aggregation, among which the most interesting and complex are biological ones. Laser biotechnology is directly related to a number of global problems of mankind, such as cancer, AIDS, environmental protection from pollution, etc. Among the wide range of issues considered in the framework of modern laser biotechnology, one can single out:

- laser surgery and destruction of biological tissues;
- laser therapy;
- laser diagnostics

Solid-state lasers are widely used in various applications: for micromachining in the semiconductor industry, in the heavy and steel industry, in medical applications. Ceramic lasers are now one of the fastest growing areas of research and development for solid-state lasers. Polycrystalline ceramics consists of many single-crystal grains 10-100 μm in size, separated by thin (~ 1 nm) boundaries. Modern ceramic samples make it possible to obtain an output power of a solid-state laser higher than 100 kW (Fig. 1) in a quasi-cw mode with a semiconductor diode pumping [1]. Recently, there has been great interest in the preparation of highly transparent ceramics Y2O3 (yttrium oxide) and YAG (yttrium-aluminum garnet Y3Al5O12), doped with Nd3+ and Yb3+ ions, as well as in the creation and study of the properties of lasers based on them. The wavelength of laser radiation determines the mechanism

of action of laser radiation on biological tissues, and, accordingly, the field of medical applications of lasers. In dermatology, there is an acute issue of finding means and methods of treatment that are safe and do not have side effects, including those that do not cause allergic reactions. Laser radiation in this area is extremely attractive. So, for example, laser radiation at a wavelength of 1.064 microns is used to remove pigmentation in the dermis, and the second harmonic of 0.532 microns, allows you to remove pigmentation on the epidermis. All this makes it extremely important to develop solid-state lasers in this region of the spectrum with stable characteristics and a long service life.

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OPTIMIZATION OF MOLECULAR METHODS FOR SCREENING ANALYSIS OF MEDICAL-RADIATION ASPECTS IN INVERTEBRATES AS TEST SYSTEMS *IN VIVO*

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Optimization of molecular methods for screening analysis of radiation-induced biological effects and mechanisms of exposure in invertebrates in vivo has been analyzed. Basically, study of reactive oxygen species and antioxidant protection enzymes are carried out at the cellular and tissue levels [1; 2]. Therefore, of particular interest is the transition to the analysis of mechanisms in vivo and the creation of an effective and affordable test system for primary screening.

The invertebrates crustaceans *Daphnia magna* and flatworms planaria *Dugesia tigrina* were as models organisms. They have several advantages like these a short life cycle (for *D. magna* is 2 months), numerous offspring, which makes it possible to analyze several generations in a short time [3]. *Planaria* is a of regeneration medicine. They have 30% of stem cells [4]. Using them as the test-organisms we modified the in vitro MTT-assay. This method is used for the integral quantitative analysis of the viable cells pool and the antioxidant enzyme system. According to our data the exposure at a dose of 10 Gy leads to a significant decrease in the MTT index [4]. This confirms the effectiveness of using modified methods of molecular biology at the organizational level. This also demonstrates the possibility of their effective application in the analysis of radiation-induced effects at therapeutic doses in vivo in invertebrates as a test model. We have modified the methods for evaluating the activity of catalase, superoxide dismutase and peroxidase enzymes as described in the cells and tissues of mollusks [5], insects [6], plants [2] and mammals [1], as well as quantitative analysis of

malondialdehyde [1]. A detailed analysis of the modification of the techniques will be presented.

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MELANOMA AND SKIN LESION DETECTION BASED ON ACTIVE CONTOUR METHOD

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The paper presents the results of improving the diagnosis of melanoma using image processing based on the active contour method.

Melanoma of the skin is a malignant tumor belonging to the category of high-grade neoplasms [1]. The risk of melanoma is 20 times higher among people of the Caucasian race compared to representatives of the black race, which is caused by the protective effect of the pigment. The average annual rate of morbidity growth over 10 years was 3.07% for men and 3.54% for women. In 2016, 1710 men and 1991 women died from skin melanoma in Russia. In the same year, 19 cases of melanoma were registered in patients under the age of 17 [2]. One of the features of melanoma is the rapidly increasing aggressiveness of this disease as it progresses. The earlier the melanoma is detected, the higher the probability of a positive long-term prognosis for the patient.

To highlight the entire area of the object of interest on images with skin neoplasms obtained using a dermatoscope, the method of active contours was used. In addition to the main contour of the neoplasm, the method allows you to select a contour with hyperpigmentation of the skin.

The proposed method allows you to clearly distinguish the boundaries of the object of interest in the image not only of the neoplasm, but also of the entire area with hyperpigmentation (Fig. 1), which allows you to accurately calculate the parameters of the entire neoplasm and increases the probability of correct diagnosis.

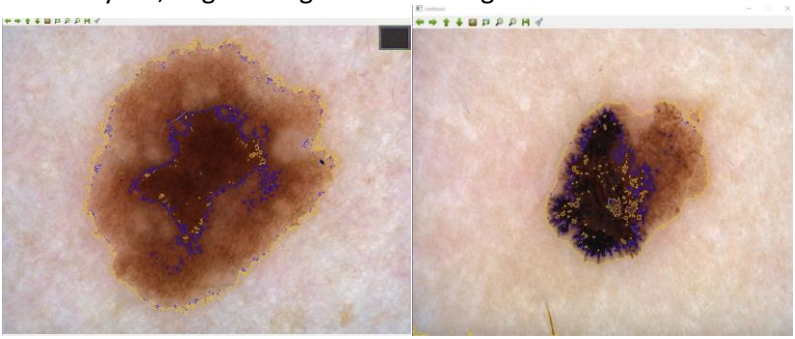

Fig.1. Experimental result of using the active contour method to isolate skin neoplasms

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T2 MAP SEGMENTATION INTO THE DEEP, INTERMEDIATE, AND SUPERFICIAL LAYERS WHEN STAGING OF PATELLAR CARTILAGE CHONDROMALACIA

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Objectives

T2 mapping is seen to be promising method for detection and staging of chondromalacia [1,2]. Various biochemical and biophysical processes might be involved in cartilage degradation in different cartilage zones. Thus, the aim of the study was investigation of T2 relaxation times separately in the deep, intermediate and superficial layers depending on the severity of chondromalacia.

Materials and Methods

171 (15.1±1.8 years) patients with mild and severe patellar chondromalacia and 51 healthy controls (14.7±2.2 years) underwent MRI examination including axial T2 mapping (TSE, 6 TE from 13 to 78ms, voxel size 0.4×0.4×3 mm). T2 were quantified from whole cartilage and with layer segmentation (рис. 1). One-vs-rest logistic regression was used to create the classification model for chondromalacia severity determination.

Results

In the superficial layer, there were found no differences between groups. In the deep and intermediate layer, the T2 significantly increases with the degree of chondromalacia. In contrast, for the whole cartilage only severe chondromalacia shows significant increase in T2 values. Sensitivity and specificity of the created classification model increases

with the growth of the feature number from 58% and 52% for the whole cartilage assessment to 69% and 61%.

Conclusion

Consideration of the differences in the water concentration, collagen matrix organization and anisotropy in the different cartilage zones by the segmentation into layers can significantly increase the clinical efficiency of the T2 mapping. This approach increases sensitivity and specificity of chondromalacia stage determination by 17% compared with whole cartilage assessment.

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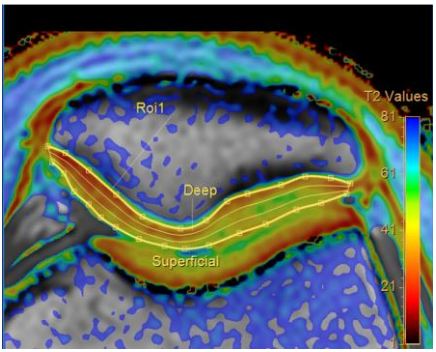

Fig. 1. An example of a T2 map of the patella cartilage with the ROI countered and segmented into three layers

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PHOTODYNAMIC THERAPY FOR BILE DUCT CANCER UNDER FLUORESCENT VIDEOSYSTEM CONTROL WITH USING CHLORIN E6

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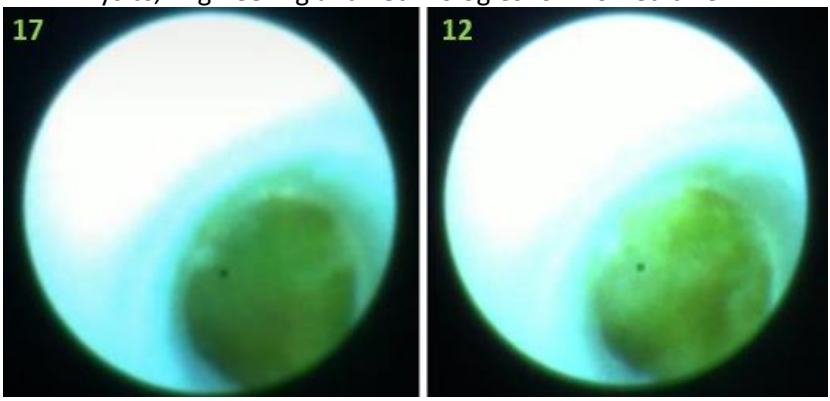
Bile duct cancer is diagnosed at late stages with localization in hard-to-reach places, where surgical intervention is possible in about 20% of patients. The reason for this is the frequent penetration of the tumor cells into the vessels of the liver gate and its parenchyma, the presence of purulent cholangitis, biliary cirrhosis and other complications of the main process [0].

The aim of the work is improving the treatment efficiency of unresectable bile duct cancer based on photodynamic therapy (PDT) under fluorescent diagnostics (FD).

The study includes patients diagnosed with Klastkin's tumor, who have been treated underwent combined minimally invasive treatment. Chlorin E6 (Ce6) was used as a photosensitizer at 1 mg/kg dose intravenously.

Intraoperative videofluorescence diagnosis was performed before and after PDT for assessment Ce6 photobleaching. Video fluorescent images of the tumor area were obtained. The level of photosensitizer accumulation in the tumor tissue is shown by the level of its fluorescence intensity (Fig. 1).



a) b)

Fig.1. The fluorescence images of bile duct cancer: a) before PDT; b) after PDT

PDT session was performed with 100 J/cm^2 influence and 50 mW/cm^2 power density. Photodynamic effects produce photochemical reaction with formation of singlet oxygen, which affects tumor cells, causing their destruction.

The use of a minimally invasive method for the PDT treatment of Klastkin's cancer under intraoperative fluorescence diagnostics control makes it possible to expand the possibilities of providing palliative care for unresectable tumors and for functionally inoperable patients. and reduce mortality from this disease.

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PERSONALIZED PHARMACOSAFETY OF THE LACRIMAL SYSTEM DURING RADIONUCLIDE THERAPY

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The lacrimal system is a complex structure, which consists of two parts: a tear production system and a tear removal system.

The lacrimal system contains a medical isotope with every method of radionuclide therapy. For example, when diagnosing the functional state of the lacrimal pathways, dacryoscintigraphy (lacrimal scintigraphy) is used - a technique consisting in studying the kinetics of 99mTc-pertechnetate in the lumen of the lacrimal pathways. This method is safe and does not entail side effects associated with the direct action of radioisotopes in the tear ducts [1]. Radioiodine therapy with 131-iodine of differentiated thyroid cancer is associated with the risk of secondary obliteration of the tear ducts in 9% of cases with a single radiotherapy, and with repeated radiotherapy - in 24% of cases [2].

Objective. To develop methods for the prevention of secondary obliteration of the lacrimal pathways after therapy with radioactive iodine.

Materials and methods. The work was carried out in several stages: the design of the study, the study of the private pharmacokinetics of radioactive iodine I-131 in the human lacrimal apparatus, the development of methods for processing scintigraphic images, the development of methods for the prevention of secondary obliteration of the lacrimal tract. According to the developed design, by means of the SPECT/CT dataset of 200 scintigraphic images was carried out. The criterion for inclusion in the study is the presence of high-dose therapy with radioactive iodine I-131 for thyroid cancer in the anamnesis, and the exclusion criteria are a repeated course of radioiodotherapy, signs of endocrine ophthalmopathy, and surgical interventions on the tear ducts in the an-

amnesis. Xeleris software was used for data processing. Data analysis was performed in the Prism program. The results of the study were entered into MS Excel spreadsheet. To develop a technique for processing scintigraphic images, the assessment of the accumulation of radioactive iodine in the structures of the tear ducts was carried out according to the following algorithm: visualization and isolation of the submandibular glands, visualization of zones accumulating radiopharmaceuticals, measurement of distances from the segment characterizing the submandibular glands obtained in paragraph 1 to the studied areas. It is assumed that as a preventive measure, drugs that have an effect on organs accumulating radiopreparation, vasoconstrictive drugs, drugs, occluders or a combination of these methods can be used.

Results. Within the framework of the study, a technique for processing scintigraphic images of the head and neck using I-131 was developed, geometric features of the areas of the lacrimal system were determined, the reliability of the differences in the areas was proved.

Conclusions. The developed method of processing scintigraphic images is the basis for creating a decision support system for prescribing a technique for preventing secondary obliteration of the tear ducts, for example, using medications, drops, occlusion of tear points, or prescribing a set of any methods.

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DEVELOPMENT OF A MODEL FOR ASSESSING THE ASYMMETRY OF THE SHAPE OF A PIGMENTED SKIN NEOPLASM

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This paper presents the results of the development of a visual method of recognition of skin neoplasms based on the asymmetry assessment model of the shape of a pigmented neoplasm.

Melanoma incidence tends to increase during the last decades. Malignant melanoma is a lethal form of skin cancer. The average annual increase in the number of cases in the Caucasoid race is 3-7% [1]. In Russia, the average annual growth rate was 2.75%, which is lower than the world average. [2] It should be noted that melanoma occupies a special place among malignant skin tumors. Thus, being structurally less than 5 % of all forms of malignant skin diseases, melanoma is the cause of more than 80 % of deaths in the group of skin neoplasms [3].

Images of pigmented skin neoplasms acquired with a dermatoscope were considered as initial data. To analyze the images we used a model of asymmetry coefficient calculation calculated with regard to the principal axes of inertia of a neoplasm which makes it possible to obtain values independent from the angle of image rotation.

The obtained asymmetry coefficients shown in the graph (Fig. 1) enable us to attribute the images under study to "melanoma" and "non-melanoma" classes with high accuracy.

The proposed model differs from the existing ones [4] in single-valuedness of asymmetry coefficients determination. The adequacy of

the model was tested on 60 images of skin neoplasms among which 20 images with the "melanoma" class were identified.

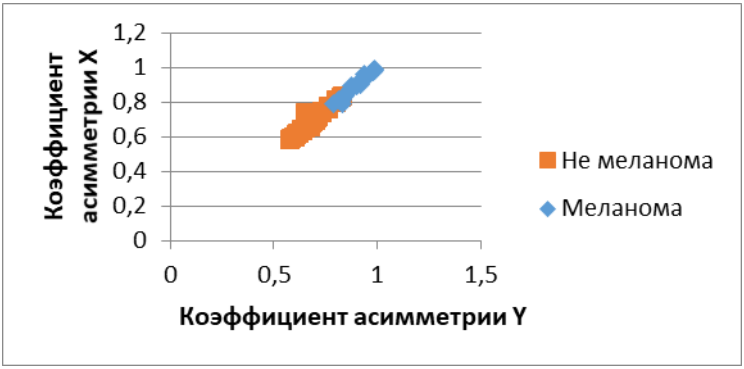

Fig. 1. Coefficients of asymmetry in the shape of skin neoplasms

Experimental results have shown that between the values of shape asymmetry coefficients for malignant and benign neoplasms we can choose a threshold value and divide "melanoma" and "non-melanoma" classes with 90% accuracy.

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