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(MOSCOW ENGINEERING PHYSICS INSTITUTE)

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# **4th International Symposium and International School for Young Scientists on “Physics, Engineering and Technologies for Bio-Medicine”**

October 26-30, 2019

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The International Symposium and International School for Young Scientists on «Physics, Engineering and Technologies for BioMedicine» is held annually by the Institute PhysBio at MEPhI in Moscow (Russia). The Symposium and School 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.

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## **4th International Symposium and International School for Young Scientists on “Physics, Engineering and Technologies for Biomedicine”**

The 4th International Symposium and International School for Young Scientists on «Physics, Engineering and Technologies for Bio-Medicine» will be held in Moscow, Russia, October 26-30, 2019 under the auspices of the Russian Ministry of Science and Higher Education, the Russian Ministry of Health and the State Atomic Energy Corporation ROSATOM. The Symposium is organized by the Institute of Engineering Physics for Biomedicine (PhysBio) of the National Research Nuclear University MEPhI (Moscow Engineering Physics Institute) in close collaboration with National Medical Research Radiological Center of the Ministry of Health of the Russian Federation and non-profit partnership «Kaluga pharmaceutical cluster».

### **Conference topics**

The Symposium aims at bringing together leading scientists and experts in nuclear medicine, biophysics, bio-photonics, and emerging fields to present their achievements in the format of the invited lectures on the following topics:

- Advanced materials and methods for MRI and PET
- Bioimaging technologies and materials
- Bio-photonics for diagnosis and therapy
- Bioprinting
- Brachy-, Proton and Ion therapy methods
- Diagnosis methods, today and in the future
- Immuno-therapy
- Isotopes for medical applications
- Medical-biological aspects of radiation effects
- Nanomaterials for biomedical applications
- Plasma and laser technologies for biomedicine
- Translational medicine

The Symposium provides a unique opportunity for fruitful scientific discussions and for establishing contacts with scientists all over the world.

### **Official Language**

The official language of the conference is English.

The format of the Symposium – invited lectures and poster sessions.

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***4th International Symposium and  
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***INVITED LECTURES***

4th International Symposium and School for Young Scientists on  
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## **NANOMEDICINE: CHALLENGES AND OPPORTUNITIES**

**Paras N. Prasad**

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This talk will address some Key Challenges in Nanomedicine and present a discussion of the opportunities to address them. These challenges and possible directions to overcome them are:

### **1) Limit of Light penetration in Optical imaging and light based-Therapies.**

The questions posed and possible solutions discussed are:

Can we use light in optical transparency windows?

Can we use photon transformation to produce on-site needed photons?

Can we use deep tissue penetrating RF, Ultrasound or X-Ray instead?

### **2) Hypoxia in Tumor making it resistant to therapy.**

The questions posed and possible solutions discussed are:

Can we deliver oxygen or produce oxygen in-situ to alleviate Hypoxia?

Can we use therapy not affected by hypoxia?

### **3) Lack of Multimodal tandem therapy to treat multidrug resistance.**

The questions posed and possible solutions discussed are:

Can we have a multi-therapeutic nanodelivery platform for controlled and staged release or activation? Do they produce synergistic enhancement of therapy?

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**4) Lack of effective and safe delivery platform for Nuclear Nanomedicine.**

The questions posed and possible solutions discussed are:

Can we produce a targeted nanodelivery system to in-situ produce nuclear therapy?

Can we generate on targeted site, high local concentration of nuclear agents?

Is the therapeutic action highly localized to prevent damage to healthy tissues?

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## **INTERACTION OF RED BLOOD CELLS IN PRESENCE OF ENGINEERED NANOPARTICLES ASSESSED BY OPTICAL TWEEZERS AND SEM IMAGING**

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Nowadays, nanoparticles (NPs) are widely used both in fundamental and applied research. A vast range of applications, from new materials for construction and energy harvesting to agricultural and cosmetic industries benefit from the use of NPs. One of the exciting emerging areas of research with potentially high impact on the society is nanomedicine [1]. It promises a custom-tailored, individual approach to patients, opening fascinating opportunities to enhance diagnostics and therapy of a plethora of diseases.

Since many NPs for drug delivery are intended to be directly injected into the bloodstream, one of the important issues to consider is how NPs interact with the blood components, in particular, with red blood cells (RBCs) (Fig. 1).

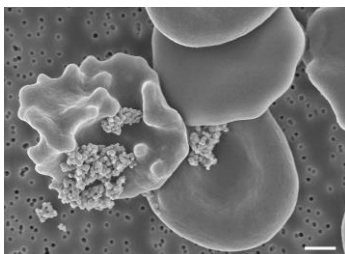


Fig.1. Scanning electron micrograph of red blood cells interacting with TiO<sub>2</sub> nanoparticles. Discocytes and echinocytes are presented. Scale bar: 1 micron.

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The methods so far applied to study such an interaction, are traditional modalities limiting the number of studied phenomena: among them are RBCs sedimentation observed with a CCD camera, morphology of RBCs visualized by optical microscopy, scanning electron (while fixed cells) and transmission electron (sections of fixed cells) microscopy. Compromised integrity of RBCs resulted in hemolysis is assessed optically either by absorption of the leaked haemoglobin within the blue-green spectral range or by fluorescent microscopy indicating presence of certain dyes inside cells penetrated through damaged cell membranes; aggregation of the cells is usually observed by a conventional microscopy.

Our experiments were performed on RBCs in autologous blood plasma incubated with different NPs -  $\text{TiO}_2$ ,  $\text{ZnO}$ , nanodiamonds and polymeric nanocapsules [2]. Formation of RBC aggregates was observed with conventional microscopy (as a reference), while quantitative interaction force measurements between individual RBCs was assessed with optical tweezers (OT). OT measurements were complemented with scanning electron microscopy (SEM) to reveal diversity in NP attachments to RBCs and their localization on the membrane together with morphological changes caused by RBCs-NPs interactions. Among tested NPs, nanodiamonds caused increasing the number of aggregates in RBC suspensions, increase in the RBCs interaction force and strong membrane surface modifications, compared to other tested NPs and control samples. The other NPs did not cause any adverse effects on RBC properties, confirming their biocompatibility and applicability for drug delivery purposes.

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## COMPLEX STRUCTURED LIGHT IN TISSUE DIAGNOSIS

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In turbid tissue-like scattering medium the conventional polarized light, scattered multiple number of times, is depolarized, and the depolarization rate depends strongly on the size and shape of scattering particles, as well as on the number of scattering events. In fact, the structure of light can be more complicated when the polarization of light across the laser beam can be radially or azimuthally polarized and carry orbital angular momentum. When these structured light beams, such as cylindrical vector beam (CVB) and/or Laguerre-Gaussian (LG) beams, propagates through a turbid tissue-like scattering medium, either anisotropic or inhomogeneous, the spin or angular momentum are changed that leads to spin-orbit interaction. The spin-orbit interaction leads to the mutual influence of the polarization and the trajectory of the light propagation. We investigate the applicability of using CVB and LG beams for optical biopsy. In current presentation propagation of CVB and LG beams in anisotropic turbid tissue-like scattering media is considered in comparison to conventional Gaussian beams. We demonstrate that by applying CVB and LG beams the contrast of visibility becomes at least twice higher in comparison to the conventional tissue polarimetry approach. Both experimental and theoretical results suggest that there is a high potential in application of structured light beams in tissue diagnosis.

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## **LASER-ABLATIVE SYNTHESIS OF FUNCTIONAL NANOMATERIALS FOR BIOMEDICAL APPLICATIONS**

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The presentation will overview our on-going activities on laser ablative synthesis of novel biocompatible colloidal nanomaterials and their testing in biomedical tasks. Our original approach is based on ultra-short (fs) laser ablation from a solid target or already formed water-suspended colloids to fabricate “bare” (ligand-free) nanoparticles (NPs) with well-controlled size characteristics [1-3], as well as coating of nanomaterials by functional molecules (dextran, PEG etc.) during the ablation process [4] or afterwards [5]. The presentation will describe different approaches to achieve appropriate characteristics of plasmonic (Au, TiN) and semiconductor (Si-based structures) nanomaterials and overview their biomedical applications. In particular, we show that bare laser-synthesized Au NPs can provide unique opportunities as SERS probes for identification of biological species such as yeast [6] and bacteria [7] based on strong local electric field enhancement and exceptional purity of laser-synthesized NPs. We also show that bare metal nanoparticles synthesized by laser ablation can provide an order of magnitude better response in glucose oxidation tasks, which promises their use as electrocatalysts in bioimplantable therapeutic devices [8], as well as overview applications of plasmonic nanomaterials (TiN) in phototherapy tasks [9]. We finally overview applications of Si NPs, which exhibit a unique combination of biocompatibility and biodegradability options [10,11]. In particular, we show that laser-synthesized NPs can be used as efficient markers in tasks of linear [12] and non-linear [13] optical bioimaging. In addition, these nanoparticles can be used in mild cancer therapies, e.g. as sensitizers of radiofrequency radiation-based hyperthermia

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**LASER FOR NANO (BIO-MEDICAL)  
(PIONEERING PULSED LASER SYNTHESIS OF COLLOIDS)**

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During the past several decades, “small-particle” research has become quite popular in various fields of physics, chemistry and in biomedical. By “small particles” are meant clusters of atoms or molecules of metals, semiconductors and others materials, ranging in size between single atoms or molecules and bulk materials.

In the year 1992 it has been assumed, that all substantial facts and technologies regarding nanoparticles were already known.

We have been using methods: Pulls radiolysis, Stop flow techniques, and chemical synthesis in liquid system, in solutions, chemical dissolution of big particles to small nanostructures.

What more was left besides tuning of existing manufacturing technologies and developing clever applications?

Could lasers be put to a good use?

That work of ours which you are calling as the pioneering one, which incited interest in the studies by other researches and was gradually developing as a new area of nanotechnologies ANGEL, leading into the area of biomedicine, was, in fact, some kind of a crazy attempt.

At that time we did not expect that this idea would have such an enthusiastic following.

Available laser technology development was working with the pulse duration of the order of nanoseconds and entering the picosecond region was only at its infancy.

Gradually I arrived to a conclusion that achieving a breaking progress quite often depends on courage to realize some crazy looking idea.

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(I do remember very well my first steps in a nuclear research that during exposure of samples with electrons on a linear accelerator, a big problem was the darkening of glass as a undesirable effect. Application of this idea was a realization of the glass at front of the New National Theatre in Prague (1977-1982), (patent was awarded).)

Attempts were made, but without any particular breakthrough...

At that time, we aimed to new type of nanostructures and we really had not expected that usage of lasers could bring us something revolutionary.[1]

But there was a surprise waiting around the corner...

We hoped that by an absorption of intense laser beam by a solid state material, producing temperature of plasma of many thousands kelvins (similar like in sonochemistry, where several thousand kelvins are reached in oscillating gas bubbles in a liquids [2]), similar effects could be reached.

Nothing more, nothing less. Where are we now and what's next?

Open the research mainly for biomedical and biomedicine applications.

For example, only this way can be prepare Fe /Ag magnetic nanoparticles, with high purity, which are at top interest for research against HIV virus and strategically defence against gram-positive bacteria like anthrax (our attempt).

See the lecture....

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Laser, small-particle, clusters of atoms, Pulsed radiolysis, Stop flow techniques

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**NANO - THE NEXT DIMENSION.  
COMBINE THE ARTIFICIAL SYSTEMS WITH BIOMEDICAL  
PROBLEMS.**

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**Organized metal nanoparticles on InP for environment gas sensors.**

Formation of stable reproducible high-barrier metal/InP interfaces is an essential prerequisite for development of various electronic devices. In particular, high quality metal/InP interfaces are demanded for good performance of InP based gas sensors. Recently, sensors of hydrogen-gas or nitrogen-oxide-gas based on metal/InP interfaces have been reported. Gas sensors have been used for industrial process controls, for the detection of toxic environmental pollutants, in human health, and for the prevention of hazardous gas leaks, which comes from the manufacturing processes.

Recently, perfection of Pd/n-InP interface has been achieved in context with fabrication of sensors for hydrogen detection by employing technology of electroless plating. A new hydrogen sensor based on Pd/n-InP interface has been fabricated by electrophoresis deposition of nanosized Pd particles. This kind of sensor shows a high sensitivity and rapid response, which prevail over devices fabricated by other methods.

This talk is to refer about the progress in the project with the central goal to find reproducible procedures for fabrication of metal/InP interfaces with improved properties for gas sensors of hydrogen on n-type InP and of nitrogen oxide on p-type InP. Metal/InP interfaces will be made by preparation of organized metal nanoparticles using electrophoresis techniques of metal deposition from metal-in-oil colloid solutions.

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Colloid solutions of Pd sphere nanoparticles have been prepared. An electrophoresis cell has been constructed and structures of Pd nanoparticles on InP surface have been made. The structures have been characterized by capacitance-voltage measurements, Normarski microscopy and secondary mass spectroscopy.

**Gold nanorods: synthesis, characteristics and applications.**

The gold nanorods are interesting because of their non-symmetric shape split into two modes: transversal and longitudinal. This gives a control over the optical properties of the rods.

This leads to application as very sensitive biosensors based on localized surface plasmon resonance. Gold nanorods were prepared by means of the seeded growth method.

The nanorods are very promising material, and much effort is now put into self-assembling them to form superlattices and photonic crystals. This would open new ways of developing sensors based on the SPR effect - not in uniform metal layer, but in photonic crystal. This would dramatically increase their sensitivity.

**Interaction artificial objects with biological environment - activation of gold nanoparticles surface.**

At contact of artificial surface with biological environment happen always to fast deposition of biological matters, mainly proteins, with which then reacting others components of environment. These phenomena they are sources of expressive problems while using artificial system in biotechnology and medicine, consequence is, nonspecific response of biosensors, activation coagulation of blood (thrombokinesis), inflammatory processes and dispraise transport of drugs and genetic information.

Perspective policy for solving these problem is based on coverage artificial object by synthetic or natural molecules, which taking nonspecific interaction (non-fouling). On such a modified surface, they are then join biological active substances, handling requisite function of system.

**Plasmon Sensors. Our, own results.**

## FEMTOSECOND LASER ABLATION OF TRANSPARENT CRYSTALS

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Optimization of ablative laser technologies calls for detailed knowledge of laser-matter interaction mechanisms resulting in breakdown and expelling of materials exposed to high-power laser pulses. Femtosecond ablation is known to be a versatile and effective tool to produce nanoparticles in a well-controlled way. The transparent NP are of particular interest for biomedical applications. For example, the nanocrystals doped with rare earth ions, featured by effective luminescence in the transparency window of the biological tissues, can be used in bioimaging; while converting of metals into the form of transparent oxides, in many cases, allows to resolve the problem of toxicity of the metal-based nanoformulations.

It seems any material can be ablated by femtosecond pulses but particular mechanisms of ablation are crucially dependent on variety of factors like parameters of laser pulses, the ambient and nature of the irradiated material. In our study, we focus in interaction of femtosecond IR, visible and UV pulses with the conventional oxide optical materials, namely the crystalline quartz, sapphire and magnesium oxide. The ultra-fast photo-electron kinetics is known to plays the clue role in deposition of energy into the lattice of a transparent dielectric resulting, in the long run, in breakdown or surface ablation.

We used two-pulse pump-probe approach in the experiments when the first pulse in the couple is tailored to generate free electrons via multiphoton absorption, while the second aims to probe characteristics of

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intraband absorption induced by these electrons. The pulsewidth, wavelength and delay between the two pulses could be varied. Two-pulse ultrafast interferometry was used for *in situ* monitoring of the free electron concentrations. Simultaneously, the optical absorption induced by the first pulse was measured by means of the transmission imaging technique. Variety of ablation thresholds was measured in the same experimental conditions with respect to the electron concentrations induced by the first pulse in the couple. Energy of the electrons within the conduction band was estimated in similar configuration of the two-pulse photo-electron spectroscopy experiments. This way, the complete set of direct measurements was performed for quantitative characterization of all stages of the kinetics ending up at the surface ablation in these materials.

The obtained experimental data and the results of theoretical modeling indicate the intraband absorption and the following electron-phonon relaxation to play the clue role in laser ablation of optical crystals known for long free electron lifetime ( $\text{Al}_2\text{O}_3$  and  $\text{MgO}$ ). Cascade intraband transitions followed by relaxation of energy via electron-phonon coupling bring the lattice to thermal instability. The detailed features of impact ionization were revealed in  $\text{SiO}_2$  known for fast trapping of free electrons and formation of STE.

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**SILICON BASED NANOTHERANOSTICS**

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Silicon nanoparticles (Si-NPs) are biodegradable without specific cytotoxic effects and they possess a lot of promising properties for biomedical applications. For example, Si-NPs can act as labels in bioimaging and sensitizer for mild therapy of cancer. These properties allow us to use Si-NPs as novel nano-agents in theranostics (therapy + diagnostics) of cancer at the nanoscale, i.e. nanotheranostics [1,2].

Aqueous suspensions of porous Si-NPs are fabricated by high-energy milling of porous Si (PSi) films formed by electrochemical etching of crystalline silicon (c-Si) wafers in hydrofluoric acid solutions [1]. Non-porous crystalline Si-NPs are prepared by different physical methods as laser-ablation [2], silane decomposition, plasma-assisted synthesis etc.

Si-NPs with efficient photoluminescence were explored as bioimaging nanolabels *in vitro*. A comparison between the fluorescent images obtained under laser excitation and white light illumination showed that PSi NPs were localized into the cell cytoplasm [3,4]. Nonlinear optical bioimaging in regimes of the second-harmonic generation and two-photon excited luminescence was found to be possible for Si-NPs with sizes above the quantum confinement regime because of an enhancement of the nonlinear optical response due to the local field effects [5].

*In vitro* experiments showed that photoexcited PSi-NPs suppressed the proliferation of cancer cells and it was explained by oxidizing properties of singlet oxygen sensitized by PSi-NPs. These results demonstrate that PSi-NPs can be considered as a sensitizer for the photodynamic and photothermal treatments of cancer and other tumors [1,3].

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PSi-NPs irradiated by therapeutic ultrasound (US) were found to cavitation-induced damages of cancer cells and tumors [3]. PSi-NPs were also loaded by anticancer drug-doxorubicin (DOX) and tested to suppress cancer tumor growth *in vivo*. DOX-loaded PSi NPs were found to result in a strong suppression of the tumor growth and prolongation of the mice' viability. The effect was stronger when the mice additionally were irradiated with therapeutic US. The obtained results indicate that PSi-NPs are promising for applications in sonodynamic and combined therapy of cancer [1,3]. Furthermore, PSi NPs with hydrophilic-hydrophobic surface properties were found to be prospective contrast agents for both the US imaging [6] and US-stimulated hyperthermia [7].

Aqueous suspensions of PSi- and Si-NPs could be efficiently heated by therapeutic radiofrequency (rf) electromagnetic radiation. The NP-sensitized hyperthermia was used for treatment of Lewis lung carcinoma *in vivo* [8]. The rf-heating sensitized by PSi-NP was demonstrated to be efficient for spatiotemporal triggering of antitumor drug release [9]. Besides, Si-NPs were found to be safe and effective carriers of <sup>188</sup>Re radionuclide for the cancer therapy by means of the nuclear nanomedicine [10]. Moreover, Si-NPs with a high density of electron spin centers have been found to be potential contrast agents for MRI diagnostics [11,12].

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## **NEW SILICON-BASED PHOTOELECTRIC SENSORS FOR MULTIDISCIPLINARY APPLICATIONS**

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A recently patented concept of silicon-based photoelectric sensor arrays will be presented. Our sensing approach is based on measuring of minority carrier lifetime in silicon by using a microwave-induced photoconductive decay as shown in Figure 1. A pulse of the infrared (IR) laser (904 nm) generates free electron-hole pairs under illuminated area close to the front surface of a silicon wafer (penetration depth of the laser radiation in silicon is about 30  $\mu\text{m}$ ). Since the free electrons and holes recombine, their concentration and, consequently, conductivity of the silicon sample decreases exponentially in time after the action of the exciting light pulse. The decaying conductivity can be monitored by detecting microwave reflectivity ensured by the photo-generated free charge carriers as a function of time. The measured reflectivity decay is fitted with an exponential curve and the obtained time constant ( $\tau_{\text{meas}}$ ) corresponds to the effective lifetime of the photo-created charge carriers in the given position of the silicon sample. Changing the illuminated zone of the studied sample allows creation of its 2D map in terms of the lifetime values  $\tau_{\text{meas}}$ , which depend on silicon parameters and its surface

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chemistry. If a silicon sample is put in an intimate contact with a chemical substance (liquid, for example), a new  $\tau_{\text{meas}}$  map induced by the substance molecules interacting electronically with silicon surface will be obtained. Thus, one can establish a correlation between a surface distribution of the  $\tau_{\text{meas}}$  values obtained for the given substance/silicon interface and chemical composition of the liquid substance.

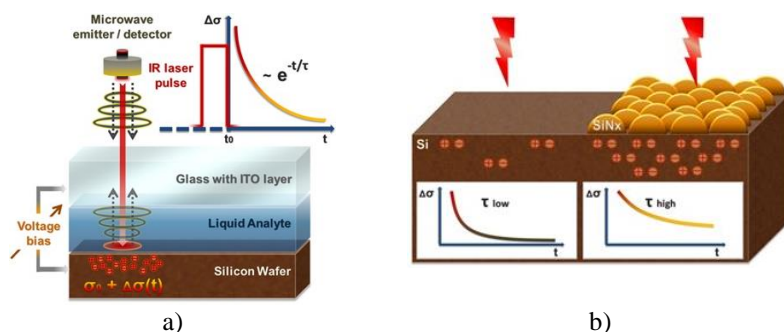


Fig.1. a) basic physical effects and measurement methods used in the photoelectric sensor arrays; b) chemical modifications of silicon surface leads to different lifetimes of photo-generated charge carriers.

The silicon-based sensor structure can be efficiently applied for a label-free and nonspecific recognition of various analytes and biological cell imaging. In particular, the lifetime of photo-generated charge carriers is confirmed to be an extremely efficient physical parameter ensuring high sensitivity of the structures to play a role of an electronic screen reflecting the complex physico-chemical interaction between the bare or partially covered silicon surface and studied chemical substance. This new kind of electronic analytical systems is an inexpensive and environmentally friendly combinatorial electronic sensing platform that is able to create characteristic electronic fingerprints of liquids, detect and recognize them.

**LIGHT-MATTER HYBRID STATES AND CONTROL OF  
CHEMICAL AND BIOLOGICAL REACTIONS UNDER THE  
STRONG LIGHT-MATTER COUPLING**

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Light-matter coupling between the molecular dipole transitions and a confined electromagnetic field provides the ability to control the fundamental properties of coupled matter such as the rates of chemical and biological reactions, efficiencies and distances of the energy transfer on the nanoscale, etc. [1]. Hybridization of energy states of molecular excitons and electromagnetic modes in cavities or plasmonic nanostructures leads to the formation of new polaritonic states with the properties which are significantly different from that of the original uncoupled states. The use of tunable optical microcavities for electromagnetic field confinement allows one to affect the coupled state properties in a controllable manner, whereas the coupling strength strongly depends on the transition dipole moment and a mode volume of the cavity. Strong dependence of polaritonic state properties on electromagnetic mode characteristics leads to the ability to control them using tunable microcavity modes [2]. Importantly, achievement of the strong coupling regime for biological molecules having low and non-oriented dipole moments paves the way to plenty breakthrough applications.

In our previous studies we have developed tunable microcavity cell (TMC) based on unstable Fabry-Perot resonator [3] which provides an

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ability of precise control of the volume of the mode, the quality factor and the spectral position of the mode at the nm-scale [4]. These properties of TMC enable direct measurement the dispersion of polaritons in transmission as well as in emission of the light [5].

In most studies, authors use ensembles of molecules with large dipole moments or highly oriented aggregates in order to increase the light-matter coupling strength, what allows one to achieve strong coupling even with the use of optical microcavities with relatively large mode volumes [1]. However, biological and, in general, organic molecules have relatively low and non-oriented dipole moments. For this reason, the strong coupling regime has been previously regularly reached using the extremely localized plasmonic modes, what significantly limits the potential of practical applications of advanced coupled systems. In our study, we have demonstrated, for the first time, an ability of realization of strong coupling regime for organic molecules with low and non-oriented dipole moments placed in the developed TMC and characterized in full fluorescence emission properties of created system. Such approach can be used for control of chemical and biological reactions and creation of novel sources of coherent spontaneous emission.

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## **NANOSTRUCTURED MATERIALS AND PHOTONIC TOOLS FOR BIOMEDICAL APPLICATIONS**

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At the present time a new direction of theranostics associated with using of nanostructured multifunctional carriers is developed rapidly. Application of nanostructured carriers is limited by absence of methods for its in vivo visualization with sufficient spatial resolution and significant tissue penetration depth [1]. One of the methods that allows to visualize and to detect the nanostructured carriers efficiently is a photoacoustic (PA) method. PA approach allows to use the photoacoustic cytometry in vivo [2]. It is also very important for detection and killing of free circulating cancer cells required for early cancer diagnostics and decreasing the metastases probability [3]. Chemical targeting was achieved by surface modification using targeted molecules [4]. Physical targeting is provided by magnetic field gradient [5] or laser tweezers [6]. The most of important requirement to the carriers is safety that including biodegradability and absence of toxicity [7]. Visualization of two types of nanostructured carriers produced by LbL assembly method was demonstrated recently in diluted and undiluted blood [8]. It was established that hollow microcapsules exhibited greater photoacoustic signal comparing to core-shell type of microparticles with the same composition of polymeric shell [8]. It was demonstrated for the first time, the super (giant) PA contrast of BNCs both in vitro and in vivo [7]. The obtained data suggest the high PA contrast of BNCs that can be associated with synergistic plasmonic, thermal and acoustic effects, especially in nonlinear mode with nanobubble formation in overheated absorbing layers, in particular gold nanoclusters between two light transparent

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shells [7].

The other type based on composite indocyanine green/polymer have using self-quenching effect has been successfully prepared and characterized in vivo and in vitro by fluorescent and optoacoustic tomographies. The combination of LbL and FIL methods [9] can be allow us to obtain the particles exhibited both PA and FL signals. This type of nanostructured carriers has a very good perspective for clinical applications agree high safety and the easiest scaling up for their preparation methods [10]. The analysis of published articles allows to make the following conclusions related to the most perspective contrast agents. It should be multimodal and multifunctional and using such type of physical phenomena as interaction of plasmonic nanoparticles and dye for quenching and enhancement of fluorescence [7], self-quenching [10], spaser effect and lasing [11].

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**FABRICATION OF PLASMONIC TITANIUM NITRIDE  
NANOPARTICLES BY FEMTOSECOND LASER**

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Capable of supporting collective oscillations of free electrons (surface plasmons), plasmonic nanostructures can offer a number of unique properties, including strong resonant scattering and absorption[1], and dramatic near-field enhancement[2,3], which makes them very promising candidates for a plethora of applications. Exhibiting a red-shifted absorption/scattering feature compared to conventional plasmonic metals, titanium nitride nanoparticles (TiN NPs) look as very promising candidates for biomedical applications, but these applications are still underexplored despite the presence of extensive data for conventional plasmonic counterparts. Here, we present the fabrication of ultrapure, size-tunable crystalline TiN NPs by methods of femtosecond laser ablation in liquids. We demonstrate the possibility to tune size of NPs between 5 and 40 nm by varying laser fluence and ablation strategies[4]. We show that so prepared TiN NPs demonstrate strong and broad plasmonic peak around 640–700 nm with a significant tail over 800 nm even for small NPs sizes (<7 nm), which is a very important fact, since this band lies within the region of relative tissue transparency, therefore laser-synthesized TiN NPs promise the advancement of biomedical mo-

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dalities employing plasmonic effects, including absorption/scattering  
contrast imaging, photothermal therapy and photoacoustic imaging.

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**HYBRID NANOMATERIALS BASED ON PLASMON OR  
FLUORESCENT NANOPARTICLES AND  
RETINAL-CONTAINING PROTEINS**

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Retinal-containing protein bacteriorhodopsin (bR) is a membrane photosensitive protein that provides transmembrane charge separation ("proton pump"), using of light energy. Applicational potential of retinal-containing proteins are so attractive that the scope of research related to their use is steadily increasing. A fundamental step in the development of devices based on such proteins is the formation of nanohybrid structures, a type of protein/nanoparticle.

The report addressed the formation of hybrid materials based on retinal-containing proteins with fluorescent semiconductor nanocrystals (quantum dots, QDs) and with plasmonic nanoparticles made of noble metals (silver, gold) [1, 2], fig.1.

The effect of nanoparticles on the efficiency of charge separation on membranes containing bR/QD hybrids was considered [3, 4]. Peculiarities of the influence of nanoparticles on the photocycle of bR and its mutant forms are discussed. The distance-dependent ability of silver nanoparticles to suppress ("freeze") the BR photocycle is considered [1,5].

It can be believed, that problems associated with the interaction of single objects (in particular, an inorganic nanoparticle with protein molecule) are very important, especially in light of the development of (scanning) probe methods and the creation of hybrid bio-nanodevices based on single objects.

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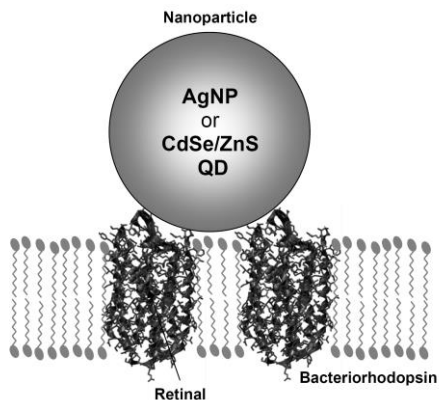


Fig.1. Scheme of hybrid bR/(AfNP or QD).

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## **BIOPHYSICAL MECHANISMS OF CHROMOSOME DAMAGE: EARLY AND DELAYED EFFECTS**

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Exposure of the cells at the G<sub>0</sub>/G<sub>1</sub> phase of the cell cycle to low- and high- linear energy transfer (LET) radiation results in induction of various types of DNA lesions. DNA double strand breaks (DSBs) are the most biologically significant molecular lesions. They can be converted into the chromatid or chromosome type aberrations in the first postirradiated cycle, termed as early aberrations. Some of chromosomal aberrations (CAs) are transmitted to the following cell cycle (as clonal stable aberrations, e.g. translocations, inversions, insertions). Other CAs, as it is usually thought, are not transmitted but results in cell death (non-clonal unstable aberrations, e.g. dicentrics, centric rings). However, the experimental studies showed the increased level of nonclonal chromosomal aberration frequency in the progeny of irradiated cells. It was recognized as the manifestation of phenomenon of radiation induced chromosomal instability (CI) which plays an important role in cancer initiation and progression. The shape of the dose response curve is the fundamental feature of any radiobiological phenomenon. Delayed aberrations follow dose-response curve which differs from that in the first postirradiation mitosis, however, the origin of this difference is poorly understood.

Here we report the results of studies of the early and delayed chromosomal aberrations in rodent cells using experimental and theoretical approaches. Early CAs of exchange type, related to DNA damage interaction-misrejoining within given chromosome, classified as intrachang-

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es, were studied by means of the new biophysical technique. This technique integrates structural information about mouse chromosome obtained with 3D genomics technology (Hi-C) providing pattern of intrachromosomal contacts and distribution of radiation induced intra-change breakpoints along the chromosome.

The delayed CAs were studied in experiments with hamster CHO-K1 cell line irradiated by  $^{60}\text{Co}$ -gamma-rays under various conditions. The CI endpoints were chosen as delayed unstable asymmetrical aberrations, or dicentrics. The observation of time and dose dependencies demonstrated the elevated level of dicentrics at many days after exposure. In addition, we searched for the modifiers of CI. Chemical inhibitors of DNA synthesis and DNA DSB repair were introduced at the first cycle after or before initial acute gamma-ray exposure. The higher incidence of dicentrics during the prolonged time course after acute exposure to radiation and inhibitors was detected indicating essential modification of CI temporal dynamics with respect to ionizing radiation only.

To explore the mechanisms of radiation induced CI in details we proposed the biophysical model of CI predicting formation of delayed dicentrics at various doses and at different times after irradiation. It was found that CI dose response for CHO-K1 cells follows curvilinear shape with sign of saturation at large doses. The biophysical model of CI predicts saturation or even plateau for CI dose response at large doses. This conclusion was verified for consistency with the data on other cell types of rodent and human origin. It remains to be established to what extent the plateau of dose response curve for delayed dicentrics is achieved for other delayed endpoints as to delayed chromatid exchanges, micronuclei *etc.* In other words, do delayed effects of different origin in various cell types display the universal behavior at large times after exposure and at large doses of low-LET radiation.

Taken together, experimental and theoretical data reveal that a process of continuous generation of DNA breaks may exist in each cell cycle of descendants of irradiated cells which is necessary to explain CI. The possible origin of continuous DNA breakage, switching on the CI phenotype, is replicative stress induced in the first postirradiation cell cycle and persisting in the progeny of irradiated cells.

**FROM STRUCTURAL STUDIES OF NICOTINIC RECEPTORS  
AND THEIR LIGANDS TO NEW DRUGS -A LONG WAY?**

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The lecture title matches “Biomedicine”, a key word of our conference, and reflects the current trend that the “receptor” is considered not so much as a target for elucidating its structure, mechanisms and role in physiology, but a target for drug design. With a particular receptor, the first question would be whether the respective gene and disease-associated mutations are known. Nicotinic acetylcholine receptors (nAChRs) are different in this respect: in previous century it has been already known that they regulate muscle contraction, and for the nAChR from the electric ray the form in the membrane has been established before the receptor subunits were cloned. In the isolation and characterization of that nAChR an important role played alpha-bungarotoxin (aBgt), a neurotoxic protein from the snake venom. It and other related snake venom alpha-neurotoxins are widely used in pharmacological analysis of different nAChRs subtypes (muscle-type, neuronal and non-neuronal) situated respectively on the muscle, nervous and immune systems. Sophisticated assistants in research on nAChRs are alpha-conotoxins, neurotoxic peptides from the poisonous snails *Conus*.

Due to wide distribution, nAChRs are implicated in versatile physiological functions (from muscle contraction to cognition) and, respectively, their functioning or malfunctioning is more or less tightly associated with the myasthenia, nicotine addiction, lung cancer, Alzheimer's and Parkinson diseases and some other.

Contemporary focusing on nAChRs as targets for drug design needs structural information about their binding sites, in particular about those where such agonists as acetylcholine and nicotine and such competitive

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antagonists as alpha-neurotoxins or alpha-conotoxins are bound. It is available, but a success with drugs is very modest. Close to strong analgesic was ABT-594, designed on the basis of epibatidine (frog toxin), but testing was stopped. Virtually the only success is varenicline which assists to refrain from smoking.

The research of the author and its collaborators for many years was focused on discovering new neurotoxic peptides and proteins and elucidating structural aspects of their interactions with nAChRs [1]. A novel linear peptide from the viper venom in preclinical studies was shown to be a more efficient myorelaxant than currently used rocuronium [2]. We recently found that oligoarginines are a new class of nAChR inhibitors [3] and this should be taken into account because these compounds are used for drug delivery into the cell.

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**LASER MICRO- AND NANOSTRUCTURING OF SOLIDS BY  
SUB-NANOSECOND LASER PULSES**

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Controlling the interactions of light with matter is crucial for the success and scalability of materials processing applications at micro and nano-scale. When lasers are used as light sources, the optimal interplay between the laser and material parameters may allow the fabrication of features with dimensions of the order or smaller than the laser wavelength diffraction limit. This report will focus on laser-assisted micro/nano structuring (NS) of surfaces and controlling materials properties via this process. A variety of different material responses have been achieved depending on the material system and the laser parameters, allowing processes to be designed and optimized to permanently alter the material's surface chemistry, crystal structure, and morphology to suite its desired function. The unique aspect of this for many applications is that the material modifications can occur over many different length scales, adding complexity to the surface and a new dimension to surface optimization. As a result, direct irradiation of materials by ultrafast laser pulses in controlled atmosphere often induces modifications leading to complex micro- and nanoscale surface structures, which are often found to have different and by far superior properties to those of the bulk materials. Indeed, we demonstrate that laser micro/nanostructured materials can be exploited for diverse emerging applications opening up new, exciting possibilities.

Furthermore, laser initiation of phase transitions at the solid-liquid interface results in the formation of self-organized micro- and/or nanostructures and high-spatial-frequency laser-induced periodic surface structures (HSFL) on the solid surface.

Formation of NS is assigned to the instability of evaporation of the liquid that surrounds the irradiated target. In comparison HSFL are occurred due to the development of thermocapillary instability of the melt layer on the target

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surface. The morphology of NS generated on various metallic as well as non-metallic bulk solids is studied as a function of laser parameters and target material.

The aim of this report to show the evolution morphology of the surface from micro (1-10  $\mu\text{m}$ ) to nanoscale (till 10 nm) as different unique types of micro and nanostructures are formed under laser ablation of target. Laser nanotechnologies presented in this topic found a lot of applications such as enhancement of external applied field up to  $10^4$  times, change of antifriction properties, development of the structured surface as ultrablack absorbers with unique optical properties. Besides presenting recent advances on the elucidation of the possible mechanisms behind the formation of the structures obtained by these techniques, it will also delineate existing limitations and discuss emerging possibilities and future prospects.

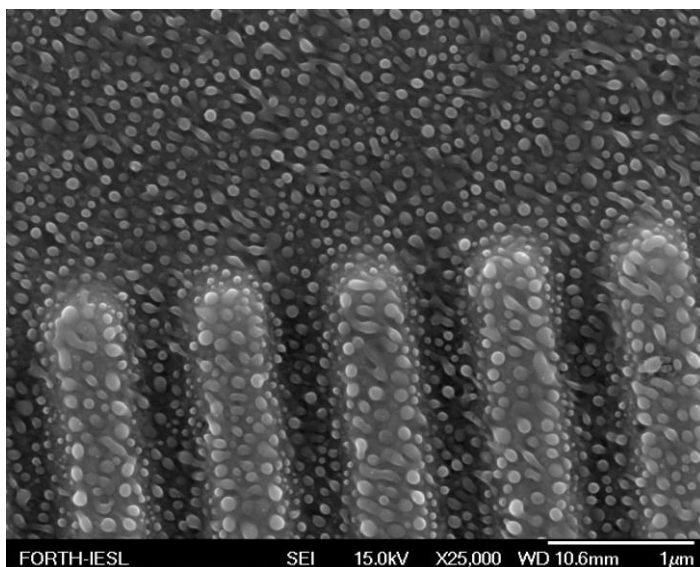


Fig.1. Self-organized nanostructures on Nickel after its ablation by 5 ps laser pulses in ethanol.

**ADVANCED TECHNOLOGIES OF NUCLEAR  
NANO-MEDICINE AND RADIOTHERAPY**

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There has been a great deal of interest in developing nuclear nano-medicine which utilizes nanoparticles (NPs) as carriers of radionuclides [1]. When functionalized by biopolymers, NPs promise safe and controllable transport of radionuclides in the blood stream, as well as a passive vectoring mechanism for targeting tumors based on their selective size accumulation (enhanced permeability and retention effect). In addition, NPs can be more heavily loaded with radionuclides to ensure an enhanced therapeutic outcome in the tumor region.

We propose silicon NPs (Si\*NPs) synthesized by pulsed laser ablation in liquids as a nearly ideal carrier of radionuclides for nuclear nanomedicine [1]. One can use these methods to make stable colloidal dispersions of silicon nanoparticles in both organic and aqueous media, which are suitable for a multitude of applications across the important fields of health care. Size tailoring allows production of Si\*NPs with efficient photoluminescence that can be tuned across a broad spectral range from the visible to near-IR.

These applications encompass several types of bioimaging and various therapies, including photodynamic therapy, RF thermal therapy, and radiotherapy. The uniqueness of such Si\*NPs is based on their biodegradability, which makes possible rapid elimination of these structures from the organism within several days even if their initial size is large (30-80 nm) under absence of any toxic effects, which was confirmed in a mice model. In addition, in contrast to Si nanostructures prepared by conventional chemical or electrochemical routes, laser-synthesized

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Si\* NPs have ideal round shape, controllable size with low size dispersion, and are free of any toxic impurities, which promises a better transport in vivo and the absence of side effects [2].

Synthesized nanoparticles were tested as carries for promising radionuclides (Re-188, Ga-68) in nuclear medicine, as well as sensitizers in radiation therapy. We demonstrate the possibility for fast PEGylation and conjugation of laser-synthesized Si\* NPs with Rhenium-188 (188Re) radionuclide, which is one of most promising generator-type therapeutic beta-emitters with the energy of positron emission of 1.96 MeV (16.7%) and 2.18 MeV (80%) and half-decay time of 17 hours [1]. We show that such conjugates can efficiently deliver the radionuclide through the blood stream and retain it in the tumor region.

We also show that Si NPs ensure excellent retention of 188Re in tumor, not possible with the salt, which enables one to maximize therapeutic effect, as well as a complete time-delayed conjugate bioelimination. Finally, our tests on rat survival demonstrate excellent therapeutic effect (72% survival compared to 0% of the control group). Combined with a series of imaging and therapeutic functionalities based on unique intrinsic properties of Si\* NPs, the proposed biodegradable complex promises a major advancement of nuclear nanomedicine.

The research was carried out with the financial support of the Ministry of education and science of the Russian Federation (agreement of November 26, 2018 № 075-02-2018-097), unique identifier of the project RFMEFI57518X0174, and State Corporation “Rosatom” (agreement of September 05, 2019 № 313/1655-D).

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## **GLIOMA METABOLISM STUDY USING <sup>11</sup>C-METHIONINE AND <sup>18</sup>F-FDG PET TRACERS**

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Differential diagnosis in brain tumors is based on stereotactic biopsy which is set as “gold standard”. This procedure is invasive and it is associated with considerable risk of complications. Moreover surgical brain intervention is expensive.

The goal of this study is to develop a non-invasive method with high specificity for diagnostic purposes. Study of brain tumor metabolism provides better understanding of glioma evolution which in its turn assists in non-invasive malignancy differentiation.

We provided two dynamic PET investigations with <sup>11</sup>C-methionine (20 min) and <sup>18</sup>F-FDG (30 min) tracers for each of 30 patient of suspected primary brain tumors. Stage of malignancy was further confirmed histologically.

Key result of the study is that grade II and grade III gliomas could be differentiated the best with <sup>18</sup>F-FDG. Though the uptake in tumor was lower than in healthy grey matter in both cases, the uptake gradient was significantly lower in grade III tumors.

Grade III and grade IV gliomas separation also benefits from additional <sup>18</sup>F-FDG study which raised specificity up to 90%.

Novel observation was that the high grade gliomas alter metabolism of the remaining unaffected part of the brain significantly. This effect was observed with both tracers.

As a conclusion we state that this new technology can directly be transferred to clinic with high benefits for the patients resulting in reduced necessity for neurosurgery and reduced costs of diagnosis.

## **MODELING OF LASER-INDUCED STRUCTURES FOR BIO-SENSING APPLICATIONS IN DIFFERENT MEDIA**

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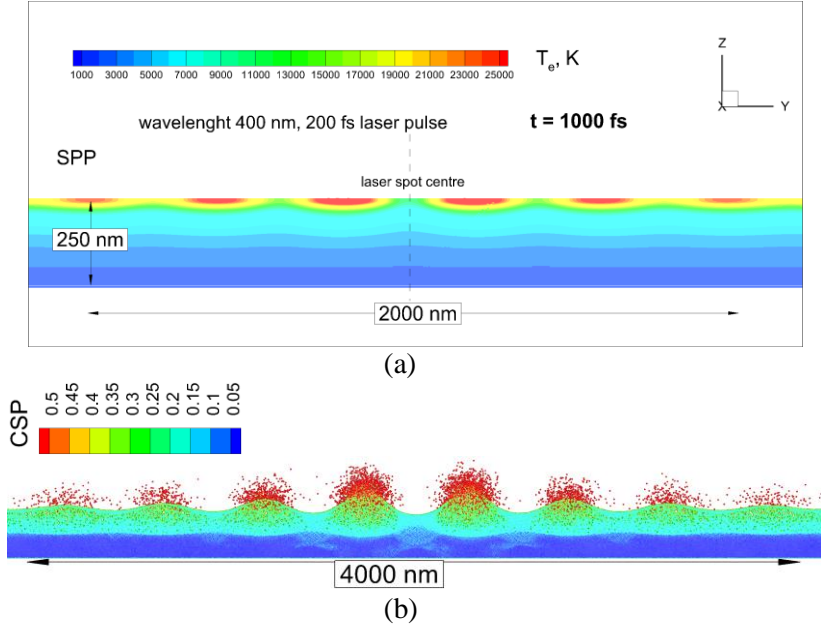
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Ultrashort laser pulses, focused on metal surfaces, can produce Laser-Induced Periodic Surface Structures (LIPSS), which have found a lot of applications in IT- and Bio- technologies. During the laser energy deposition Surface Plasmon Polaritons (SPP) [1], i.e. surface plasmons coupled to a laser-electromagnetic wave, can be excited on a rough material surface. The interference of the plasmons wave and the incoming pulse leads to the redistribution of the laser intensity across the material's surface, establishing of the periodic electronic temperature field, (Figure 1), and the subsequent formation of LIPSS.

In this work we propose a combined atomistic-continuum Molecular Dynamics based approach as an efficient numerical tool for investigation of LIPSS formation mechanism on metals in super-large simulations [2]. We introduce the corresponding source term description due to SPP in the combined model [3]. The nanostructuring mechanism is then investigated under conditions of vacuum ambient and in the regime of spatial confinement due to a thick water layer above the target. The simulation results are directly compared with the experimental data, generated on the same temporal and spatial scales, and analyzed. This allowed to extract the main mechanisms of LIPSS formation and the reasons for a higher quality of structures generated under water. The performed research allows for a possibility for the structures generation with predesigned topological, morphological, optical, and magnetic properties.

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**Fig. 1:** The resulting electronic temperature distribution inside the metal target (side view) upon 200 fs laser pulse energy deposition at the wavelength of 400 nm, due to excitation of SPP in the vicinity of the laser spot center is shown (a). The atomic snapshot of the structured surface (side view) is shown for the same modelig, taken at 75ps of the simulation time (b). The atoms are colored by Central Symmetry Parameter (SCP) for identification of the local crystal structures as follow: solid < 0.08 < defects < 0.12 < liquid < 0.25 < surface < 0.50 < vapor.

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**“PHYSICAL MARKERS” AS A PROSPECTIVE TOOL IN THE  
DETECTION OF HUMAN DISEASES**

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Despite considerable advances in understanding the biological and biochemical nature of human diseases, many biophysical aspects of changes in tissue, cells, and pericellular coat are still unclear. Here we propose a methodology based on nanoscale-resolution imaging of surfaces of cells together with collecting their physical information. Such an approach can be applied to study and detection or diagnostic of various diseases and abnormalities.

Using a combination of resonance and sub-resonance atomic force microscopy, ringing mode [1] and machine learning analysis we demonstrated that parameters, which are typically utilized in engineering to describe surfaces, can be applied to classify physical alterations of the surface of human epithelial cells. We found that the stepwise in vitro development of cancer (from normal to immortal (pre-malignant), to malignant) could be associated with the emergence of simple fractal geometry on the cell surface [2, 3]. Further, we applied this method for the detection of bladder cancer by using cells collected from human urine samples. Diagnostic accuracy of 94% achieved when examining five cells per patient's sample. It is a statistically significant improvement ( $p < 0.05$ ) in diagnostic accuracy compared to the currently used clinical standard, cystoscopy, as verified on 43 control and 25 bladder cancer patients [4].

This method can also be applied for the detection of other cancers, in which cells or body fluid are available for analysis without the need for invasive biopsy, e.g., upper urinary tract, urethra, colorectal and other

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gastrointestinal, cervical and aerodigestive cancers. Furthermore, the described approach can be extended to detect cell abnormalities beyond cancer as well as to monitor cell reaction to various drugs (nanopharmacology).

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## THE POSSIBILITY OF MULTIPARAMETRIC MRI AND PERSPECTIVES OF ARTIFICIAL INTELLIGENCE (AI) IN THE DIAGNOSIS OF PROSTATE CANCER

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**Objectives:** Assess of correlation between the apparent diffusion coefficient (ADC of the tumor, ADC ratio) and final grade group (GG) after radical prostatectomy (RP), determination of the threshold values of ADC for detecting clinically significant prostate cancer (PC) with subsequent evaluation in a prospective group.

**Materials and methods:** 118 patients with PC were included in the retrospective group. These patients underwent RP from 2012 to 2017 with preoperative 3 Tesla multiparametric MRI (mpMRT) with contrast enhancement in a single diagnostic center. After processing MRI studies, average values of tumor ADC and benign tissue ADC were calculated using ADC maps. The prospective part of the study included 60 patients with mpMRI conducted prior to prostate biopsy and subsequent RP from January 2018 to March 2019.

**Results:** Tumor ADC and postoperative GG had a statistically significant negative correlation of moderate strength (Spearman's correlation coefficient = -0.733,  $p=0.0001$ ). Similar correlation was found for the ADC ratio with a slightly higher Spearman ratio ( $p = -0.802$ ,  $p=0.0001$ ).

In the ROC-analysis of potential for discrimination between GG 1 and GG 2, the area under curve (AUC) was 0.898 (95%, CI 0.835-0.961) for tumor ADC and 0.950 for ADC ratio (95%, CI 0.909-0.992). When used as a criterion for determining GG 1 tumor, ADC values  $\geq 0.78$  shown sensitivity of 78% and specificity of 98%. When using ADC

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ratio  $\geq 0.4501$ , the sensitivity and specificity were 92 and 93% respectively. The prospective part of the study demonstrated the effectiveness of applying the obtained diffusion coefficient thresholds. When used as a criterion for determining clinically significant prostate cancer ( $GG > 1$ ), threshold value of tumor ADC had sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 81%, 61%, 73%, 77 % and 67% respectively. For the ADC ratio sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 84%, 91%, 87%, 94% and 78% respectively.

**Conclusion:** ADC of the tumor alone had a statistically significant negative correlation with the final PC grade group. ADC ratio had a stronger correlation, proving to be more accurate for the purpose of distinguishing between GG 1 and GG 2. In the prospective study, ADC ratio demonstrated high predictive value. Diffusion coefficients may prove to be a useful predictive tool with regard to the histopathological aggressiveness of PC. Integration of non-invasive markers in the diagnostic process will help with personalizing the patient's treatment plan and avoiding unnecessary risks. In the future, a combination of artificial intelligence guided study and the keen expert eye of a diagnostician will enable a more thorough detailed analysis of the MR image, providing data on the localization, architecture and aggressiveness of the prostate cancer, ensuring a more balanced approach to both the choice of treatment strategy and the necessity of surgical intervention.

**PHARMACOKINETIC PROPERTIES OF A NEW POTENTIAL  
TUMOR IMAGING AGENT BASED ON GLUCOSE  
DERIVATIVE AND GALLIUM-68**

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Tumors are characterized by increased consumption of glucose in comparison to normal tissues. Therefore, glucose derivatives can be used as carriers to deliver radionuclides directly to tumor tissue. Positron emission tomography (PET)-based imaging of the uptake of a radioactive fluorine-labeled glucose analog, <sup>18</sup>F-fluorodeoxyglucose has been successfully used in the clinic for tumor diagnosis and staging, as well as for monitoring responsiveness to treatment.

Gallium-68 (<sup>68</sup>Ga) is a promising radionuclide for PET imaging due to its nuclear and physical properties ( $T_{1/2} = 68$  min,  $\beta^+ = 89$  %,  $E_{\beta^+max} = 1.9$  MeV). It also can be obtained from <sup>68</sup>Ge/<sup>68</sup>Ga generator up to 12–18 months. In this work a new glucose derivative, <sup>68</sup>Ga-NODA-aminoglucose, was synthesized and its biodistribution was studied.

<sup>68</sup>Ga-NODA-aminoglucose was synthesized with high radiochemical yield. Radiochemical purity was obtained more than 95 %. All biodistribution studies were performed in BALB/c mice with subcutaneously transplanted colon adenocarcinoma. 10 days after tumor transplantation the animals were injected with 0.37 MBq in a volume 0.1 ml of <sup>68</sup>Ga-NODA-aminoglucose. Animals were sacrificed at 5 min, 1, 2 and 3 h post-injection (p.i.), the samples of different organs and tissues were collected. The radioactivity was measured by gamma counter. The uptake was expressed as percentage of injected dose per gram of tissue (%ID/g).

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It was observed that the highest uptake of radioactivity in tumor was 4.88 % ID/g, declined to 1.57 %, 0.54 % and 0.52 % ID/g at 1, 2, and 3 h p.i., respectively. The amount of  $^{68}\text{Ga}$ -NODA-aminoglucose in blood reached 9.83 % ID/g at 5 min p.i., but decreased later to 0.04-0.55 % ID/g, providing the ratios tumor/blood as high as 3.38-12.78. The excretion of activity occurred through the urinary system, so the accumulation of activity in kidney was 1.67-37.22 % ID/g. In other soft tissue organs the uptake of  $^{68}\text{Ga}$ -NODA-aminoglucose was low and didn't exceed its accumulation in tumor throughout the study.

In conclusion,  $^{68}\text{Ga}$ -NODA-aminoglucose is considered to be a promising agent for PET tumor imaging in addition to existing radiopharmaceuticals.

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## MULTIFUNCTIONAL NANOSTRUCTURES FOR ONCOTHERANOSTICS

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A considerable attention of researchers in the field of biomedicine is being directed toward the development of personalized medicine, especially for theranostics. Theranostics implies the combination of therapeutic and diagnostic properties on a single platform.

Here we describe the development of theranostic agents for the personalized analysis of HER2-positive cancer cells both *in vitro* and *in vivo*. HER2 is tyrosin kinase receptor and belongs to the EGFR receptor family. HER2 is a clinically relevant oncomarker which is overexpressed in 20-30% of human breast tumors. Its overexpression predicts a high risk of disease recurrence, high metastatic tumor potential, resistance to chemotherapy and reduced overall survival of patients. However, this receptor normally presented on healthy cells in a much lesser extent.

So, the precise and quantitative detection of this oncomarker has important clinical implications.

We describe the development of magnetic (1-3), silver (4), and silica-shelled (5) theranostic agents for the targeted delivery to HER2-overexpressing cancer cells as well the development of physical methods of such agents detection (6-8).

This study is a step towards the creation of new generation of theranostic agents, which are capable of affecting only certain cell types under specific conditions and act as a therapeutic agent when it necessary.

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## **STATUS OF PROTOM SYNCHROTRONS FOR PROTON THERAPY**

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Physical-Technical Center of P.N. Lebedev Physical Institute of RAS (PhTC LPI RAS) and Protom Ltd. are engaged in development and implantation of synchrotrons for proton therapy complexes into clinical practice. There are two proton therapy complexes (PTC) “Prometheus” on the territory of Russia. That are fully developed and manufactured at PhTC LPI RAS and Protom. Every day patients with head and neck cancer get treatment at PTC “Prometheus”, which is located in the A. Tsyb MRRC, Obnisk. At the moment both complexes have accumulated more than 3 years of clinical experience. In addition, two facilities are based on the PhTC LPI RAS and Protom synchrotrons in the USA. One operates in the proton center in the McLaren hospital, Flint, and another one is as part of the single-room PTC Radiance330 in MGH, Boston. Both these centers are equipped with gantry-type setups. The first accelerator complex for proton therapy in Shilat, Israel was launched in August 2019. It is also based on Protom synchrotron. The important and distinctive characteristics of this proton synchrotron: low weight, compact size and low power consumption allow it to be placed in ordinary hospitals without the construction of any special buildings.

This report presents current data on developments of the PhTC LPI RAS and Protom Ltd. That are related with proton synchrotrons. In addition, it provides data on the use of PTC “Prometheus” under the clinical conditions.

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Fig.1. General view of Protom Synchrotron at the production line in Protvino

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## NANOPARTICLE TRANSPORT ON RED BLOOD CELLS FOR TREATMENT OF LUNG CANCER

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Lung tumors are the leading cause of mortality among all cancer types, and their treatment remains a major challenge because of the extreme complexity of surgical excision of these tumors. Here we apply RBC-hitchhiking for efficient drug delivery to metastases in lungs.

Cell-hitchhiking is an approach, which uses various cells as natural carriers of drugs within the organism [1-2]. In our work we screened binding efficiency of different nanoparticles (NP) with red blood cells and showed pharmacokinetic of obtained NP-RBC complexes in organism. We observed two major changes in NP behavior. Firstly, for cationic nanoparticle, their anchoring on cell surface lead to increase of blood circulation time up to 10 times, which can be explained both stealth properties of RBC [2] and inhibition of macrophages after first interaction with nanoparticle complexes [3]. Secondly, both cationic and anionic NP, showed high delivery to lungs (up to 120-fold), if they were attached on RBC. We believe, high NP accumulation in lungs may be due to existence of shear stress between RBC-carriers and walls in small capillaries.

Then, we used the metastatic model of melanoma to demonstrate the RBC-hitchhiking capabilities for tumor treatment. For this aim, we prepared Doxorubicin-loaded chitosan nanoparticles and adsorb them on the cell surface. Although, these NP were ineffective for treatment if they circulate in free form, their delivery on RBC significantly slowed

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the growth of pulmonary metastases. We found a 3-fold decrease in the total number of metastatic nodules in 10 days after treatment.

The demonstrated technology of NP drug delivery could become a valuable tool for development of new strategies for the alleviation the course of a number of acute and chronic lung diseases.

The work was supported by Russian Science Foundation 19-72-30012 (treatment studies) and Russian Foundation for Basic Research 18-34-00834 (circulation studies).

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**MECHANISM OF LASER-INDUCED FORMATION OF METAL  
NANOPARTICLES AND NANOSTRUCTURES FOR  
BIOTECHNOLOGICAL APPLICATIONS: MOLECULAR  
DYNAMICS MODELING**

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In this work we investigate the mechanism of nanostructures and nanoparticles generation due to laser ablation of metals in liquid media with numerical atomistic-continuum model. The mode is capable of addressing the mechanisms of non-equilibrium laser-induced phase transition processes at atomic level with Molecular Dynamics (MD) approach, whereas the effect of free electrons, playing a determinant role during short laser pulse ablation phenomena, is described in continuum with Two Temperature Model (TTM). Such the combined MD-TTM model [1] was utilized in a super large scale modeling of the process of nanostructures and nanoparticles generation in water. The obtained structures and nanoparticles are then analyzed and characterized from the point of their morphology and size distribution correspondingly, Figure 1. These characteristics were then studied as functions of the laser parameters (pulse duration and fluence), the irradiated materials (Al and Au), and surrounding media (air and water) [2]. The performed simulations enable the direct comparison of the modeling results and the experimental data [3] and allow for drawing a possibility of the manipulation with the laser parameters and surrounding media for generation of the nanostructures and nanoparticles with predesigned properties. The results have a strong impact on the IT-and Bio-technologies.

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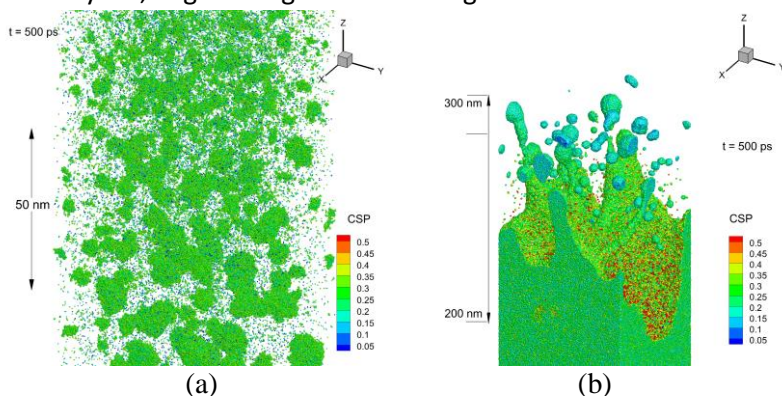


Fig.1. The atomic snapshots are shown from the modeling of laser-induced nanoparticles generation process in vacuum (a) and in liquid media (b) at the simulation time of 500ps. The 0.3ps laser pulse is directed from the top (along Z axis) at the incident fluence of  $2 \text{ J/cm}^2$ . The atoms are colored by Central Symmetry Parameter (SCP) for identification of the local crystal structures as follow: solid  $< 0.08 <$  defects  $< 0.12 <$  liquid  $< 0.25 <$  surface  $< 0.50 <$  vapor. The water atoms in (b) are blanked for visual analysis.

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## **MODERN RADIOPHARMACEUTICALS: MYTH AND REALITY**

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Radiopharmaceutical (RP) - the drug in a ready to use dosage form contains one or more radionuclides. A radiopharmaceutical is a radioactive compound used for the diagnosis and therapeutic treatment of human diseases.

RPs usually have minimal pharmacologic effect, because in most cases they are used in tracer quantities. RPs are administered to humans, they should be sterile and pyrogen-free and should undergo all quality control measures required of a conventional drug.

A radiopharmaceutical has two components: a radionuclide and a pharmaceutical. In designing a radiopharmaceutical, a pharmaceutical is first chosen on the basis of its preferential localization in a given organ or its participation in the physiologic function of the organ. Then a suitable radionuclide is tagged onto chosen pharmaceutical. After administration of the RP radiations emitted from it and detected by a radiation detector. Thus, the morphologic structure or physiologic function of the organ can be assessed.

Ideal Radiopharmaceutical for diagnostic purposes is:

- the pharmaceutical of choice should be safe and nontoxic for human administration;
- radiations from radionuclide of choice should be easily detected by nuclear instruments, and the radiation dose to the patient should be minimal;
- the radiopharmaceutical should be easily produced, inexpensive, and readily available in any nuclear medicine facility;
- short effective half-life;
- no particle emission;

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- decay by electron capture or isomeric transition;
- high target-to-nontarget activity ratio.

An ideal radiopharmaceutical should have all the above characteristics to provide maximum efficacy in the diagnosis of diseases and a minimum radiation dose to the patient.

A radiopharmaceutical for a particular organ study is designed on the basis of the mechanism of its localization in the organ.

The mechanisms of RP localization, applied in nuclear medicine [1]:

1. Passive diffusion. Examples:  $^{99m}\text{Tc}$ -DTPA in brain imaging,  $^{133}\text{Xe}$  in ventilation imaging.
2. Ion exchange. Example: uptake of  $^{99m}\text{Tc}$ -phosphonate complexes in bone.
3. Phagocytosis. Example: removal of  $^{99m}\text{Tc}$ -sulfur colloid particles by the reticuloendothelial cells in the liver, spleen, and bone marrow.
4. Capillary blockage. Example:  $^{99m}\text{Tc}$ -macroaggregated albumin particles trapped in the lung capillaries.
5. Active transport. Examples:  $^{131}\text{I}$  uptake in the thyroid,  $^{201}\text{Tl}$  uptake in the myocardium.
6. Cell sequestration. Example: sequestration of heat-damaged  $^{99m}\text{Tc}$ -labeled red blood cells by the spleen.
7. Metabolism. Example:  $^{18}\text{F}$ -FDG uptake in myocardial and brain tissues.
8. Receptor binding. Example:  $^{11}\text{C}$ -dopamine binding to the dopamine receptors in the brain.
9. Compartmental localization. Example:  $^{99m}\text{Tc}$ -labeled red blood cells used in the gated blood pool study.
10. Antigen-antibody complex formation. Examples:  $^{131}\text{I}$ -,  $^{111}\text{In}$ -, and  $^{99m}\text{Tc}$ -labeled antibody to localize tumors.
11. Chemotaxis. Example:  $^{111}\text{In}$ -labeled leukocytes to localize infections.

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## **PALETTE OF FLUORESCENT NANOPARTICLES FOR BIOLOGY AND MEDICINE**

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To date, a large number of fluorescent nanoparticles have been developed, the use of which is very promising in various fields. A variety of properties, advantages and disadvantages of different types of nanoparticles determine the choice of the type of fluorescent nanoparticles for solving certain problems. Here we review and compare the capabilities and limitations of such nanoparticles in various applications.

Potential applications of the following types of fluorescent nanoparticles are considered (Fig.1):

- fluorescent semiconductor nanocrystals (quantum dots);
- carbon graphene-like and diamond-like nanoparticles;
- polymer fluorescent nanoparticles;
- porous silicon-based nanoparticles;
- nanophosphors.

From the point of view of using fluorescent nanoparticles in medicine, their toxicity, stability in biological fluids, and the possibility of their excitation / fluorescence in the area of the transparency window of biological tissues (IR region) are of principal importance. In addition, possibilities and limitations of the fluorescent nanoparticles for photodynamic therapy, including two-photon PDT are important.

The development of new nano-instruments for medicine, based on the formation of multifunctional systems, including the functions of delivery, directed and controlled release of the drugs, as well as monitoring the process of administration, transport to targets, and therapy requires an understanding of the physicochemical properties of nanoparticles of various nature. In the work, we tried to identify the features of

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 different types of nanoparticles, systematize them and analyze their  
 properties from the point of view of developing diagnostic and therapeutic  
 nano-instruments.

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 19-14-00171).

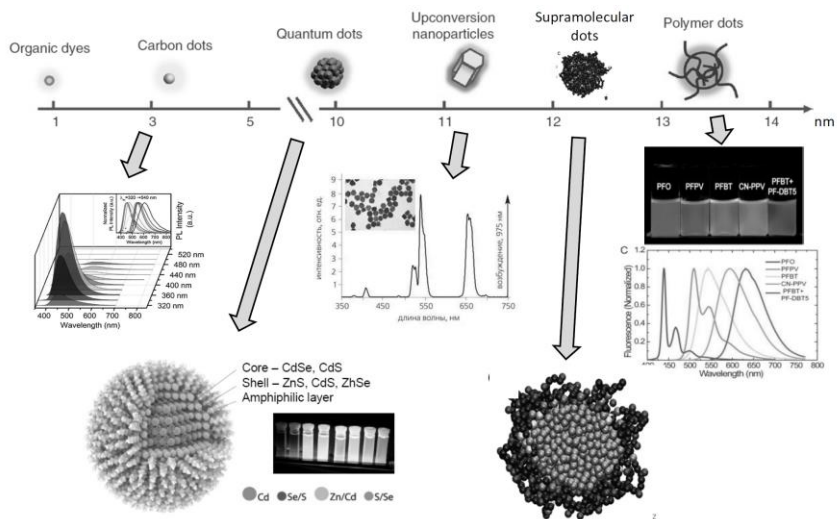


Fig.1. Fluorescent nanoparticles.

## **SUPRAMOLECULAR MULTIFUNCTIONAL STRUCTURES FOR THERANOSTICS**

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The revolutionary progress in genetic and protein engineering methods make it possible to directionally modify the molecular size, affinity, specificity, and immunogenicity of an antibody, their derivatives and analogues, oriented to the use in the diagnosis and targeted therapy of cancer. Rational design and molecular engineering allow us to model the compounds with preprogrammed properties and to create biotechnological producers of therapeutic medicines. It provides a straightforward technology to design wide range of recombinant proteins and multifunctional nanoheterostructures for the highly efficient delivery of active agents to cancer cells for therapy and monitoring of the pathological processes.

Radionuclide molecular imaging of HER2 expression in disseminated cancer provides a tool enabling personalized stratification of patients for HER2-targeted therapies. Designed ankyrin repeat protein DARPin G3 demonstrated promising features as a probe for imaging of HER2 *in vivo*. We hypothesized that position (C- or N-terminus) and composition (hexahistidine or (HE)<sub>3</sub>) of histidine-containing tags would influence the biodistribution of [<sup>99m</sup>Tc]Tc(CO)<sub>3</sub>-labeled DARPin G3. To test the hypothesis, G3 variants containing tags at N-terminus (H<sub>6</sub>-G3 and (HE)<sub>3</sub>-G3) or at C-terminus (G3-H<sub>6</sub> and G3-(HE)<sub>3</sub>) were labeled with [<sup>99m</sup>Tc]Tc(CO)<sub>3</sub>. The specificity of HER2 targeting *in vivo* was confirmed. The tumor uptake in BALB/c nu/nu mice bearing SKOV3 xenografts was similar for all four variants. On the opposite, there was a strong influence of the tags on uptake in normal tissues. The tumor-to-liver ratio for [<sup>99m</sup>Tc]Tc(CO)<sub>3</sub>-(HE)<sub>3</sub>-G3 was three-fold higher compared to the hexahistidine-tag containing variants. Overall, [<sup>99m</sup>Tc]Tc(CO)<sub>3</sub>-

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(HE)<sub>3</sub>-G3 variant provided the highest tumor-to-lung, tumor-to-liver, tumor-to-bone and tumor-to-muscle ratios, which should improve sensitivity of HER2 imaging in these common metastatic sites [1–3].

We also report our recent results on design of targeted Nano Drug Delivery Systems including gold nanorods, biological pseudomonas exotoxin A, etc. [3–7].

The research was supported by RFBR # 17-00-00121/17-00-00122.

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## **NANOPARTICLES FOR BIOPHOTONIC APPLICATIONS**

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Nanomaterials are becoming more and more popular for different applications. They are widely used in consumer products such as cosmetics, sunscreens, food, toothpastes, and paints. Industrial applications include anti-fogging mirrors, self-cleaning surfaces and solar cells. Nanostructures are found also in nature (e.g. in butterfly wings, bug shells, lotus leaves, gecko paws) and inspire scientists for creation of light-reflecting structures, anti-wetting surfaces, and strong adhesive materials. Nanotechnology can significantly increase strength of materials used in automotive, medical, construction etc. industries decreasing overall weight of components and devices. Future of personalized medicine will significantly rely on nanoparticles (NPs) as drugs or drug carriers.

In this lecture, applications of different types of NPs (semiconductor, rare-earth and gold) in biomedical optics and biophotonics are presented. In particular, the following topics are covered:

- $\text{TiO}_2/\text{ZnO}$  NPs as UV filters in sunscreens;
- $\text{TiO}_2/\text{ZnO}$  NPs as antibacterial agents;
- $\text{TiO}_2/\text{ZnO}$  NPs for biotissue-mimicking phantoms;
- upconversion particles for imaging;
- gold NPs for cells and bacteria studies.

The variety of applications utilize different size-dependent properties of NPs: dominating absorption and weak scattering in the UV spectral range for sunscreens [1]; ability to generate free radicals upon irradiation with certain wavelengths for bacteria elimination [2]; pronounced scattering in the visible and near-infrared spectral ranges (NIR) for biotissue-mimicking phantoms [3]; NIR excitation and luminescence for

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imaging of biotissue with suppressed scattering; plasmonic enhancement of spectroscopic fingerprints for identification of microorganisms [4]; ability to convert absorbed light into heat to disrupt cellular organelles for drug delivery and disease treatment [5].

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**NANOPHOSPHORUS. SYNTHESIS AND APPLICATION**

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The report describes the current state of Affairs in the field of synthesis and application of nanophosphors – nanoparticles of the composition  $\text{NaYF}_4\text{:Re}$ , where Re is a mixture of rare earth elements in certain proportions, which depend on the subsequent applications of the obtained particles. The synthesis of these objects by the example of thermolytic method with the indication of difficulties and bottlenecks of such reactions is considered in detail.

As examples of application of nanophosphors the researches in which the author of the report took part are given.

One of the directions relates to work in the field of biomedicine, where radioactive ( $^{90}\text{Y}$ ) upconverting nanoparticles (UCNPs) conjugated with recombinant target toxin DARPin-PE40 were used for synergistic effect on cancer cells. It has been shown that such a combined effect approximately 2000 times reduces the therapeutic dose of the drug required for severe inhibition of model tumor growth [1,2].

The second area of research is related to the creation of compact waveguide amplifiers for integrated optics operating in the telecommunication C-wavelength range 1530-1560 nm when pumped by light with a wavelength of 975-980 nm (downconversion). The problem of creating such amplifiers with a length of not more than a few centimeters in the world has not yet been solved. The proposed approach is based on the use of nanophosphors with the structure of doped core–unalloyed shell, covalently bound to the macromolecule of fluorinated polymers. Such nanocomposites will have high optical transparency and ultra-high quantum yield.

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## **NEW AND PERSPECTIVE METHODS AND TECHNOLOGIES OF RADIOTHERAPY**

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Radiation therapy (RT) as a method of treating cancer has more than a century of history. Over the years, it has come a long way from the first basically unsuccessful attempts to treat cancer with ionizing radiation to a powerful high-tech treatment method, recommended both as an independent method and in combination with surgery and chemotherapy for more than 60% of cancer patients. The lecture discusses how the paradigms of radiation treatment have changed, from the point of view of physics, gives a brief description of modern radiotherapy methods and focuses on the discussion of new promising radiotherapy methods and technologies.

For a long time, RT developed essentially on the basis of “trial and error,” therefore there were periods in its history when interest in it almost completely passed. Notable successes appeared in the late 30s and early 40s and the last century, when in physics the features of the interaction of ionizing radiation with matter were studied and in radiobiology the basic mechanisms of the effect of these radiation on cells and the human and animal body were discovered. Currently, RT is undergoing a period of almost revolutionary development. In the middle of the last century, the main task of physicists and technical specialists in RT was to bring the prescribed dose to the target with as little irradiation of normal tissues as possible. Now a fundamentally new formulation of the problem has become possible: irradiation of only malignant cells, wherever they are, in the absence of irradiation of normal tissues and organs.

From the point of view of dose delivery methods to the target, modern RT is divided into four main types: distance, contact (or brachytherapy), radionuclide and radioimmune RT. The lecture discusses the main areas in which currently improving the methods and technologies

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of each type of RT. These areas of competence of medical physics are the following:

- General increase in the efficiency and competitive ability of RT.
- An increase in the difference between the dose in the target and in surrounding normal tissues and critical organs.
- Decrease in the integral dose received in total by the whole organism of the patient.
- Development of methods for optimizing radiation treatment plans based on radiobiological criteria (target functions).
- Improving the accuracy of contouring of targets in order to reduce the volume of normal tissues located in the high-dose area.
- Development of methods to increase the radiosensitivity of malignant cells and reduce the radiosensitivity of normal cells.
- Development of methods for the selective irradiation of malignant cells.
- Reducing the duration of treatment and increasing the survival time after radiation treatment.

Stereotactic RT, radiosurgery, and image-guided RT are the most notable contributors to the progress and increase in the efficiency of distance radiotherapy. They make it possible to increase the accuracy of beam targeting and reduce the total time of radiation treatment. New opportunities in this direction are opened by the transition to irradiation with proton and heavy ion beams. So far, this type of radiotherapy is almost twice as inferior in price to treatment with photon and electron beams. But progress in the development of accelerator and dose-generating technologies will undoubtedly reduce this difference. Moreover, in some studies, it is shown that if we take into account the quality of life and the survival time of patients after radiation treatment, then proton treatment is now equal in price to photon radiotherapy.

Some hopes for further progress in distance radiotherapy are provided by the so-called binary methods, which include neutron capture and photon capture therapy. Recent studies show that the latter, combined with the introduction of elements with a high atomic number in the form of nanoparticles into the tumor volume, more than doubles the biological effect of radiation.

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The main feature of contact RT is a sharp dose gradient with distance from the source. This gives the advantage of contact RT compared with distance RT in respect of greater sparing of normal tissues. Recently, an alternative to radionuclide sources has been superminiature x-ray tubes.

All types of RT based on the use of external sources have a very serious drawback, namely the lack of selectivity. Patients with spreading tumor diseases throughout the body cannot be treated with surgical methods and / or distance and / or contact RT. The problem is solved if it would be possible to create such radiopharmaceuticals that selectively accumulate in the tumor, and even better attach only to malignant cells and at the same time are the medicine. This direction of RT is called targeted therapy. The main principles of targeted therapy are:

- The target volume should be determined and labeled at a biological level.
- Irradiation should only affect diseased cells, wherever they are, sparing normal cells located even in close proximity to malignant ones.

The most significant achievements of recent years in such types of radiation therapy as radionuclide radiation therapy and radioimmune radiation therapy were obtained precisely in the framework of targeted therapy.

The lecture concludes with a discussion of chemical and physical methods for modifying the radiosensitivity of cells and the body as a whole.

## NEW APPROACHES TO THE DIAGNOSIS AND TREATMENT OF BRAIN TUMORS

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During neurosurgery of brain tumors there are two main problems: lack of fast and sensitive methods to quantify structural and biochemical changes in neural tissues in vivo, need in strict detection of tumor border to provide radical resection of tumor with maximal preservation of healthy tissue. Spectroscopic studies can provide fast and accurate detection of main chromophores and fluorochrome concentration in tissue. Currently in the clinical practice intraoperative spectroscopic diagnostics is carried out sequentially - first the spectroscopic registration and then tumor destruction in approximately the same area.

The purpose of this work was to develop a method for demarcating the boundaries of intracranial tumors and equipment that implements it directly in the process and in the area of tumor removal.

As far as in the neurosurgery of intracranial tumors the main instrument for tumor destruction is an aspirator, we proposed to combine a fiber-optic spectrometer and video fluorescent endoscopic tool with aspirator cannula. A special design of the cannula was developed, containing channels for optical fibers in the walls located on the sides of the suction port. The relative position of the illuminating and receiving fibers for spectroscopy was chosen to provide spectral probing of exactly the same region in which aspiration takes place. The distal end of the channel for the video fluorescence endoscopic system is located at a

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working distance from the tissue surface, providing an overview and contrasting of the tumor in the vicinity of the removal zone.

System testing was carried out on optical phantoms, rat C6 glioma cell culture spheroids, and samples of human intracranial tumors obtained during neurosurgical operations. During the removal of a tumor from different sites (tumor center, perifocal area), the degree of in vivo fluorescence signal was determined intraoperatively using a Zeiss Opmi Pentero intraoperative microscope in Blue 400 mode. From the selected area of the tumor, biopsy material was taken (presumably homogeneous in its properties) with subsequent measurement of spectra and combined images using the developed device.

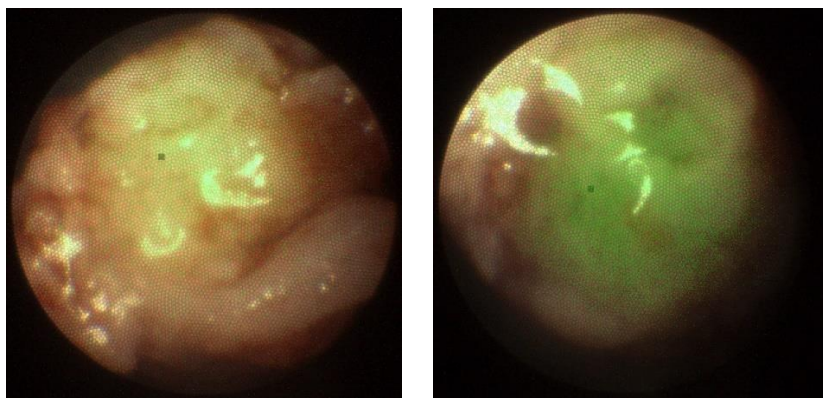


Fig.1. The combined video fluorescent analysis on intracranial tumor tissues ex vivo: 5mg/l and 10 mg/l of Pp IX were detected in tissues, which are displayed on the left and right images, respectively.

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## ***POSTER REPORTS***

**THE MAIN ASPECTS OF RADIATION THERAPY.  
COMPARISON OF 3D CONFORMAL AND INTENSELY  
MODULATED RADIOTHERAPY**

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**Urgency.** Today, the problem of cancer is of social importance. This is due to the continuing trend of increasing morbidity, high frequency of relapses and low degree of recovery, leading to a fatal outcome of patients after specialized treatment.

Despite the successes achieved in the diagnosis, currently up to 30% of the population seek medical care already with widespread stage III-IV cancer.

**Purpose of research.** Assessment of the dependence of dose distributions on various organs and tissues using the device TRUE-BEAM. Comparison of efficacy of conformal and intensely modulated radiotherapy. [1]

**Materials and methods.** TrueBeam (TrueBeam STx™)-gener-a revolutionary new technology used for the purpose of curing cancer diseases; it is one of the last modern developments of radiation therapy available in the world today. This technology is a system for controlling the conduct of radiation diagnostics, which makes it possible to regulate, take into account and synchronize the area of imaging, the position of the patient. It allows the most accurate and complete radiotherapy course, and including to exercise control over the treatment process in the dynamics. This system, created by Varian [2], combines a huge number of innovations that make it possible to use all the latest and modern techniques in the field of radiation therapy, including radiotherapy with a camera of observation (IGRT and IGRS), as well as radio-

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therapy with density regulation (IMRT).[3] the Dosing speed of this device exceeds 8 times the dosage of standard linear accelerators.

**Summary.** Comparison of the characteristics of the depth distributions obtained during measurements by the ionization chamber and the water fan and the longitudinal arrangement shows good agreement of the measurement methods. The most accurate methods of dose delivery to a particular location were identified, taking into account the density and uniformity of dose distribution. Work continues on the Protocol, which takes into account the child's body with the appropriate coefficients (this is not yet anywhere).

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## OPTIMAL PARAMETERS OF LASER METER OPTICAL CHARACTERISTICS OF THE CORNEA

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Today, in eye microsurgery, it is required to measure the thickness of the cornea and residual corneal layers during vision correction operations. In ophthalmology, it is required to measure the depth of the lesion with an ulcer of the anterior tissues of the eye. Also, in some cases, it is required to evaluate the value of the refractive index of transparent biological tissues. Such a thickness and refractive index meter should be accurate, contactless, fast, safe to use, and etc. In world medical practice, such a thickness meter in the process of ophthalmic surgery on the cornea is not yet available.

We solved this problem by combining the use of modified triangulation [1] and interferometric [2] laser methods. The scheme of the device is shown in Fig.1 [3]. The aim of this work is to find the optimal values for the parameters of this meter.

The mathematical model of our gauge of the thickness  $z$  (or refractive index  $n$ ) is described by the system of equations (1):

$$\begin{cases} z = k_1 \frac{2x \sin \beta_1}{M} \frac{\sqrt{n^2 - \sin^2 \alpha}}{\sin 2\alpha} \frac{\sqrt{n^2 - \sin^2 \varphi}}{n}; \\ z = \frac{\lambda L}{k_2 s} \frac{\sqrt{n^2 - \sin^2 \gamma}}{\sin 2\gamma} \sin \beta_2; \end{cases} \quad (1)$$

where  $k_{1,2}$  are the scale factors,  $M$  is the magnification of the lens,  $\lambda$  is the wavelength of laser (650 nm),  $L$  is the distance from the cornea to the screen,  $x$  is the distance between the light marks in the image (laser 532 nm),  $s$  is the width of the interference fringes on the screen,  $\gamma$  and  $\varphi$

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 are the laser angles of incidence 650 nm and 532 nm,  $\alpha$  is the laser angle  
 of viewing 532 nm,  $\beta_1$  is the CCD angle, and  $\beta_2$  is the screen angle.

The found optimal values of the angles are presented in table 1.

Table 1. The optimal values for angles in a triangulation-interferometric thick-  
 ness measurement scheme

Laser angle of incidence 650 nm, $\gamma$	Laser angle of incidence 532 nm, $\varphi$	Laser angle of viewing 532 nm, $\alpha$	CCD angle, $\beta_1$	Screen angle, $\beta_2$
41°	41°	13°	73°	69°

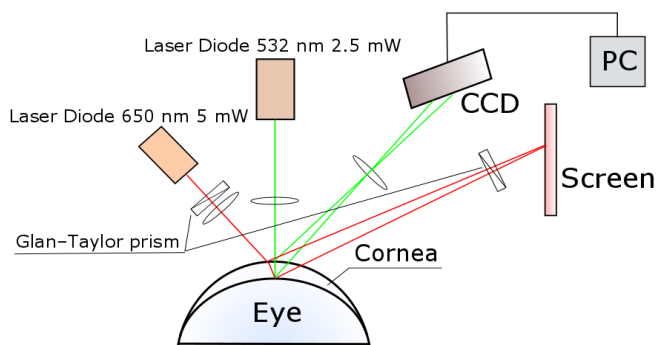


Fig.1. Experimental scheme of the laser meter [3]

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## MINIMIZATION OF THE NUMBER OF PROJECTIONS IN CONE BEAM X-RAY TOMOGRAPHY

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Reconstruction of medical images based on the obtained object projections can be solved using multiple methods. One method is an iterative method (ART, EART). The iterative method is advantageous both in terms of the possibility of improving the quality of the final image and in terms of the possibility of reducing the number of projections, which reduces the radiation burden on the volume of interest. Both of these aspects might improve the quality and outcome of radiation therapy.

Computed tomography of the patient usually performed using about 900-1000 x-ray projections. We show that the use of iterative reconstruction methods might lead to reducing the number of projections below 90-100. Thus, it becomes possible to solve the practical problem of reducing the dose burden on the patient, which might be critical both in terms of radiobiological indications (e.g. stimulated growth of some resistant tumors) and exploiting the potential for ordinary tomography to detect structural changes in the patient's body as a response to treatment.

The work is aimed at the description of the directly applied mathematical apparatus of the ART and E-ART algorithms, as well as mechanisms of minimization of the impact of reconstruction artifacts for low-angle tomography. The paper also presents the results of the analysis obtained of reconstructive images for a model (parallelepiped of a certain size with cavities) and native (human head) volumes. The characteristic artifacts of reconstruction depending on the number of iterations are shown, as well as the comparative characteristics of the suggested

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iterative method to the Feldkamp method. In addition, we demonstrate that even in the presence of an extremely small number of projections (two projections), it is possible to restore a distinctive image that preserves the size of the structures, which might be used for the task of positioning the patient.

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**PROTOTYPE DEVELOPMENT OF AN X-RAY TOMOGRAPH  
FOR THE DIAGNOSIS OF WEAKLY ABSORBING / PHASE  
OBJECTS**

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X-ray phase contrast imaging using Talbot-Lau interference principles is an innovative and promising approach to visualizing soft tissues and weakly absorbing objects. Unlike the method based on the absorption of radiation, the phase-contrast method is much more sensitive to tissue densities and structural inhomogeneities of the material. This allows it to make better images of tissues and materials with a low absorption coefficient of x-ray radiation, for example: cartilage, joints, polymers, etc. Thus, a high resolution of the setting can allow detecting malignant neoplasms in the early stages, for example, during mammography examinations.

This paper describes the development process of a tomographic setup, a method for processing X-ray interferograms, and presents the results of the experiment.

### **Introduction**

The essence of the phase-contrast image is to change the phase of the radiation when passing through a substance. The refractive index of photons is determined by the following expression:

$$n = 1 - \delta + i\beta \quad (1)$$

Where  $\delta$  - characterizes the phase shift,  $\beta$  - attenuation index. For X-ray radiation of 10-100 keV in soft tissues,  $\delta > 1000\beta$ . From which it is seen that the phase change is much more sensitive to a change in the soft tissue than to a change in intensity.

To obtain a phase-contrast image, we use a tomograph based on the Talbot-Lau interferometer. The Talbot-Lau interferometer is based on the effect of the same name. When a plane wave is incident upon a periodic diffraction grating, the image of the grating is repeated at regular

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distances away from the grating plane. The regular distance is called the Talbot length, and the repeated images are called self-images or Talbot images.

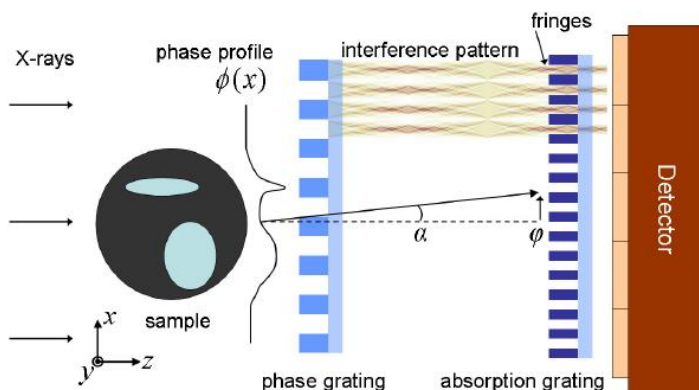


Fig.1. Experimental scheme of a tomograph based on the Talbot-Lau interferometer

The principle of operation of the installation is as follows. When coherent radiation passes through an object, the object changes the phase of the radiation wave. As a result, the interference pattern is changing. Thanks to this change, we can measure the phase change of the wave and build a phase map of the object.

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## SIMULATION OF INSULIN-GLUCOSE CONCENTRATION DYNAMICS

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Glucose is the primary energy source for human's cells. Its' blood level is controlled by the insulin-glucose regulatory system. In the system working correctly, there is an adequate amount of insulin produced to maintain the glucose level. If something goes wrong, diabetes and other dangerous diseases might develop.

To understand the basic principles of mutual influence of “glucose-insulin” under different conditions, both experimental [1] and theoretical [2] researches are being carried out. There are two noticeable time delays in the dynamics of glucose and insulin in the human's organism. The first one is related to the electric actions inside the beta cells, since insulin needs time to cross the endothelial barrier [3]. The second one is related to the effect of insulin effect on glucose release from the liver [4].

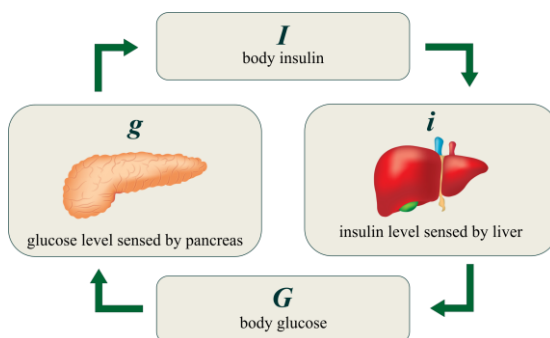


Fig.1. Incorporation of time delays in our model.

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We modified mathematical model [2] to include the two time delays (see Fig. 1) to get a better understanding of what are critical factors in normal and abnormal work of insulin.

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t)) \cdot f_4(i(t)) + f_5(i(t))$$

$$\frac{dI}{dt} = f_1(g(t)) - d \cdot I(t)$$

$$\frac{dg}{dt} = f_6(G(t)) - B_2 \cdot g(t)$$

$$\frac{di}{dt} = f_7(I(t)) - D_2 \cdot i(t)$$

The model analysis showed results, consistent with experimental data [1]. Besides, our model allows predicting some changes in the work of the glucose-insulin regulatory system in both a healthy organism and obesity.

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## PRECISE FLUORESCENT DIAGNOSTICS OF CERVICAL NEOPLASMS FOR PHOTODYNAMIC THERAPY

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The method of photodynamic therapy (PDT) is one of the newest, organ-preserving methods of treating tumors. However, it is necessary to develop a diagnostic method that would allow controlling the process of photodynamic therapy by changing the fluorescence intensity for effective photodynamic therapy.

**Aim.** To develop a method of precise fluorescent diagnostics (FD) of internal female genital organs (cervix, cervical canal, vagina) for PDT.

**Materials and equipment.** Chlorin e6 (Photolon) at a dose of 1 mg/kg was used as a photosensitizer (PS). The fiber spectrometer LE-SA-01-BIOSPEC with the PS excitation using He-Ne laser ( $\lambda = 632.8$  nm,  $P_{\max} = 15$  mW) and semiconductor laser ( $\lambda = 660$  nm,  $P_{\max} = 1.5$  W) was applied for precise FD. PDT was performed using the semiconductor laser ( $\lambda = 660$  nm,  $P_{\max} = 1.5$  W) 3 hours after a drip intravenous administration of the PS. The two-channel video-system [1] was employed to obtain fluorescent images of the studied normal and pathological tissues.

**Results.** The fluorescent images of the cervix and vagina at the applied dose of the PS had high contrast between normal and pathological tissues. The ones obtained by a video-system have allowed estimating the PS concentration parallel measured with the fiber spectrometer. Tak-

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ing into account the fact it was possible to control the PS concentration in the irradiated tissues by fluorescence, the doses of light energy was changed based on the fluorescence intensity and amounted to 100–200 J/cm<sup>2</sup>. Video-fluorescent diagnostics of the cervical canal in this configuration was uninformative. The diffuser used for PDT provides sufficiently uniform irradiation, however, does not allow controlling the treatment effectiveness via photobleaching. The use of angular optics is required to solve these problems.

**Conclusions.** The combined use of video- and spectral-fluorescent diagnostics for cervical and vagina neoplasms during PDT has shown good correlation between the obtained values, which allows for better estimation of the treatment process and, if it is necessary, the change of tactics.

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## IN VITRO STUDIES OF SILICON NANOPARTICLES AS PHOTOSENSITIZERS FOR LASER-INDUCED HYPERTHERMIA

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Silicon nanoparticles (Si NPs), including nanocrystals silicon is widely investigated for applications in Biomedicine, in particular for theranostics (simultaneous diagnosis and treatment) of oncologic and other socially significant diseases [1-3]. Silicon (Si) nanoparticles (NPs) are promising for biomedical application due to the fact that they have low toxicity and can be eliminated from the body by biodegradation.

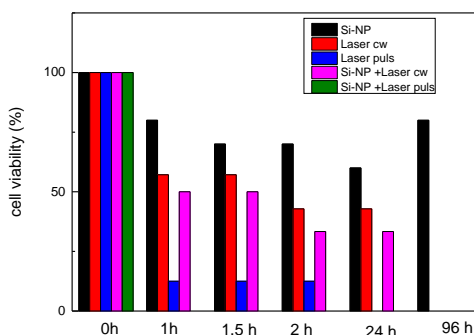


Figure.1. Viability of Paramecium Caudatum cells under laser irradiation conditions

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The method of laser ablation was used to obtain Si nanoparticles, femto-second laser irradiation was used to obtain them. *Paramecium Caudatum* were selected to analyze the toxicity of nc-Si and to study the effect of continuous and pulsed wave long laser radiation (808 nm) on living organisms. *Paramecium Caudatum*, despite the simplicity of the organization, combine the characteristics of a single cell and a whole organism.

It was shown that Si based NPs can be used in cancer therapy as drug carriers, sensitizers of ultrasound and high frequency electromagnetic radiation. Control of the NPs accumulation in the tumor after intravenous administration is crucial for the effectiveness of therapy. The best results can be achieved when the NPs can be controlled and simultaneously used in therapy. For the analyze of the Si NPS particles toxicity and to study the effect of continuous and pulsed longwave laser radiation (808 nm) on living infusoria of *Paramecium Caudatum* was selected.

We found that silicon nanoparticles alone do not exhibit significant toxicity in given concentrations, nevertheless, application of pulsed laser radiation to them leads to reduction of cell viability. This results should be improved by optimization of Si NPs concentration and pulse parameters to enhance the effect of sensitization without negative side effects of irradiation and NPs exposure alone.

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## **LASER DEPOSITION AND STUDY SURFACE AND LUMINESCENCE NANOPARTICLES AND FILMS SI**

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The abstracts are devoted to a research the laser deposition and study surface and luminescence of the films and nanoparticles Si, which under certain conditions can activate molecular oxygen and burn biological objects. This effect can be used to detect cancer cells in photodynamic therapy.

The thin films and nanoparticles Si were prepared by PLD/MBE-2000 deposition installation and Coherent/Lambda Physik COMPex PRO 110 excimer laser [1, 2]. It is recommended for the formation of nanoparticles and films Si: laser operates at repetition rates 15 – 105 Hz at 100 – 250 mJ per pulse (248-nm, KrF) for an average power output of 3 – 25 Watts. Range of He or He + N<sub>2</sub> working pressure were from  $5 \cdot 10^{-3}$  to 5 Torr. The spectrums of luminescence were shot in spectrograph Mightex CCD Spectrometer USB 2.0, blue laser 450 nm MingNuo OptoElectronicCoLtd and were recorded by the MSS matrix.

Figure 1 provides a dependence on the intensity of luminescence (a.u.) depending on the wavelength of radiation. Thus, work was carried out on a laser installation to prepare Si films to create photo-excited nanoparticles.

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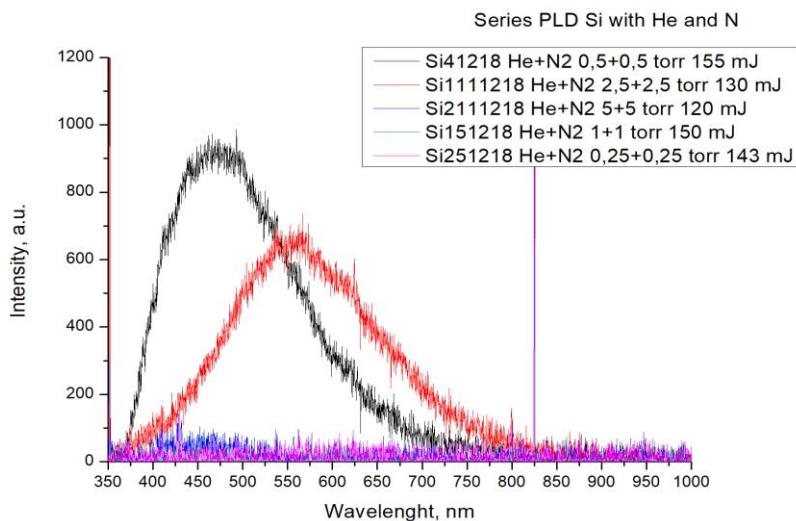


Fig. 1. Dependence of luminescence intensity (a.u.) depending on the wavelength of radiation

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#### Acknowledgments

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## **LIPID-CONTAINING NANOPARTICLES AS A VEHICLES OF DRUG DELIVERY SYSTEMS**

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*Lomonosov Moscow State University*

This work is dedicated to solving an urgent scientific problem - the creation of a fundamental scientific base of technology for the controlled delivery and release of drug and biologically active substances in living systems. The urgency of this problem is due to the need to create new highly effective methods of drug therapy that provide targeted delivery and spatiotemporal control of drug activity in local target areas of the body. The development of such methods will provide a radical increase in the effectiveness of the use of drugs and a decrease in their negative side effects. The aim of my work is to develop new vehicles of targeted delivery of drugs and biologically active substances based on colloidal lipid-containing particles, which are mimetics of lipoproteins - biogenic carriers of hydrophobic molecules in the human body. Directly in this work, new lipid nanostructured magnetic colloidal systems are created and investigated, which will be carriers of water-insoluble drugs in the aqueous phase, the spatial localization of which can be controlled using an external magnetic field. At the moment, a technology has been developed for the synthesis of nanostructured lipid nanoparticles with the inclusion of magnetite nanoparticles and model drug compounds in their composition, which in the future can be used as vehicles of controlled targeted delivery of a number of medicinal and biological active substances. The analysis of the obtained lipid nanoparticles using a complex of methods of structural diagnostics: atomic force microscopy and transmission electron microscopy. This work was supported by the Russian Science Foundation (project 18-29-02080).

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**ANTHROPOMORPHIC MALE PHANTOM’ DOSE  
ESTIMATION FOR APOLLO MISSION ASTRONAUTS WHEN  
CROSSING THE EARTH RADIATION BELTS**

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During space flights astronauts are exposed to space radiation. The main dose commitments at quiet Sun is formed by the passage of the Earth radiation belts (van Allen belts), the remaining dose provides by galactic cosmic rays (GCR) and solar cosmic rays (SCR). In this work we estimated the “Apollo” mission astronaut’s radiation exposure with the help of computational models: (a) anthropomorphic male phantom of “MIRD Humans” [1] series, and (b) precise radiation transport model (by the MCNP code [2]). Together with the universal transport code MCNP, the nuclear data library received by the TALYS nuclear reaction simulation program was used. The belt passage scenario is taken from the available literature data [3]. A comparative analysis with the data from the official “NASA” report [4] was carried out

The calculation model of the command module with the astronaut, presented in figure 1, consists of 175 surfaces, that are combined using Boolean algebra into 46 cells and as a result, 43 organs of the human body are simulated. The command module is a sphere of aluminum with a thickness of  $7.5 \text{ g/cm}^2$  – the equivalent thickness of the command module shielding [5].

Protons and secondary radiation generated during proton transport form ~ 90% of the dose, the remaining 10% is provided by X-ray radiation. Proton energy is in the range from 20 to 1000 MeV. The radiation transport model takes into account a wide range of secondary particles. Contributions of all energy degradation chains to the calculated flux functionals for all particles were taken into account up to the boundary energy of 1 keV (the lower energy of particles in the data library).

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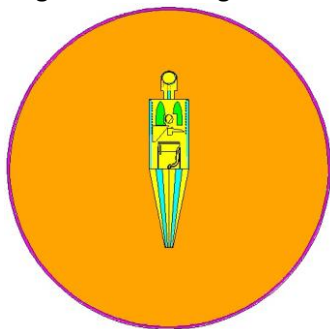


Figure 1 – Calculation model of the “Apollo” command module with an anthropomorphic astronaut phantom

The main dose commitments in the male phantom are received by the reproductive organs. The equivalent dose in other organs is tenths/hundredths of Sievert. The average value of the dose equivalent is 2.07 Gy. The received value of the effective dose is 5.8 Sv. It can be concluded that the results depend on the choice of the van Allen belt scenario passage, taking into account various factors such as geometry of irradiation and shielding, as well as the chosen method of calculation.

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## **POROUS SILICON BASED NANOCONTAINERS FOR PROSPECTIVE ANTITUMOR DRUG**

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Porous silicon (PSi) prepared by electrochemical etching of crystalline silicon (Si) is a promising material for biomedical applications because its biodegradability, low toxicity and ability to act as an agent for different therapeutic modalities [1]. Moreover, PSi nanoparticles (NPs) were successfully tested in vivo as nanocontainers for anticancer drug as doxorubicin [2,3]. While doxorubicin is well water soluble and rather efficient even without nanocontainer's delivery, it does not effective against chemotherapy-resistant cancer stem cells [4]. Another promising antitumor drug is salinomycin, which is a polyester ionophore antibiotic. The ability of salinomycin to efficiently eliminate cancer stem cells and induce partial clinical regression of highly treated and therapy-resistant cancers has been clinically proven [5]. However, salinomycin is not well soluble in water that complicate its application in the chemotherapy of cancer. The objective of our work is to create nanocontainers based on PSi-NPs for the delivery and controlled release of salinomycin.

Aqueous suspension of PSi-NPs with given sizes about 100 nm were prepared by high-energy ball-milling of electrochemically prepared mesoporous layers. The pore morphology and chemical composition of the coating of the inner surface of pores in PSi-NPs were investigated by means of the electron microscopy and optical spectroscopy. Then, the prepared NPs were loaded with salinomycin by mixing its saturated

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aqueous solution and suspension of PSi-NPs at a certain mass ratio of the drug and NPs. The next step consisted in separation of the insoluble fraction, washing with water the resulting nanocontainer filled with the drug, and their subsequent drying. The above described procedure allowed us to obtain powder of PSi-NPs loaded with salinomycin.

It was checked that the prepared nanocontainers being dispersed in aqueous medium resulted in gradual release of salinomycin. The free salinomycin concentration in water was measured by using Fourier infrared spectroscopy in attenuated total reflection mode. The release rate was found to be dependent on the PSi/Salinomycin ratio during the nanocontainer preparation (see Fig.1). The nanocontainers with larger initial loading with salinomycin exhibited its slower release for 6 h.

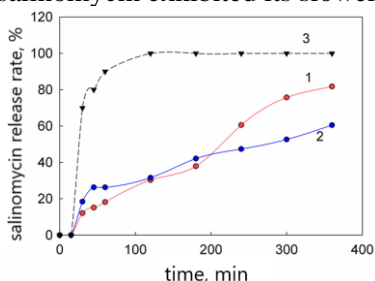


Fig.1. Temporal dependences of the released salinomycin from PSi-NPs with different PSi/Salinomycin ratio as 1:1 (1), 1:2 (2) and 2:1 (3), in water at 37 ° C.

The revealed possibility of slow drug release from nanocontainers is promising for both local mild chemotherapy of primary tumor and killing cancer stem cells.

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**FEATURES OF PENCIL BEAM SCANNED PARTICLE  
THERAPY OF INTRAFRACTIONALLY MOVING TUMORS:  
A SHORT ANALYSIS**

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Recently the pencil beam scanned particle therapy such as proton or heavy ion therapy is the most actively developing method of radiation oncology. The main advantages of this method are higher accuracy, better dose conformation, lower radiation load on healthy tissues and higher LET and RBE rates (for heavy ions) than in case of conventional photon therapy. These ones are based on the fundamental features of interaction of the accelerated heavy charged particles with matter and high-tech patient immobilization and beam delivery systems. In clinical practice there are already a lot of confirmations of these advantages [1].

Nonetheless, benefits of particle therapy can be achieved only in case of complete immobility of the CTV, for example, for head and neck cancer. In case of other prevalent localizations in thorax and abdomen areas, such as lung, liver, breast, prostate and others, the sufficient precision may not be obtained. It is due to intrafractional motion of the tumor and internal organs caused in the main by cardiac work and respiration. This motion leads to distortion of planned dose distribution in the CTV, to emergence of hot and cold points, i.e. areas with overdosage and underdosage respectively, to increase in radiation load on healthy tissues and vital organs [2-3].

In conventional photon radiotherapy a similar problem already has enough solutions in the form of various methods and techniques, such as: expansion of CTV-PTV margins, using of mechanical compression; real-time monitoring of tumor position with the help of various respira-

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tion sensors, radio-opaque fiducial markers and X-ray systems, electromagnetic transponders; treatment planning based on 4DCT; irradiation in modes: breathing-hold, gating, tracking and etc [1-2]. However, it can be very difficult to implement a direct transfer of these methods to pencil beam scanned particle therapy due to a number of factors.

Firstly, the motion of internal organs leads to a change of density in the beam path that causes a shift of Bragg peak from calculated position. Secondly, there is an inconsistency between motion of the scanning beam and the target volume [3]. Thirdly, the radio-opaque markers and electromagnetic transponders can limit the possible angles for beam delivery and can distort dose fields [2]. Fourthly, a pattern of the tumor motion, in general, is complex and represents a combination of translational, rotational movements and deformations, and also depends on the tumor parameters: dimensions, location and etc [2-3]. Fifthly, the respiration and cardiac cycle is usually unstable in time, phase and amplitude so higher tumor motion monitoring and irradiation accuracy is required. Sixthly, the treatment planning is carried out based on X-ray CT whereas proton or heavy ion CT can not only have a higher density resolution, but also will allow us to get information about the stopping properties of tissues in the beam path [2].

All these factors can substantially influence on the treatment planning, tumor motion monitoring and irradiation. Therefore, a close cooperation of physicists, engineers, oncologists and others is necessary for both a large-scale research, optimization of the existing strategies in the context of particle therapy and development of the new ones.

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## **INTERPRETATION OF READINESS POTENTIAL BY USING THE BCI FOR MANAGING BIONIC SYSTEMS**

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**Keywords :** EEG, BCI, bionics, neurophysiology

### **Research Project Description**

#### **Relevance**

In modern neurophysiology, there is a global problem associated with the interpretation of EEG signals, i.e. at the moment there is no full-fledged map of interpretation of encephalogram signals. Our proposed technical solution will help partially solve the presented problem. The introduction of neuro-computer interface technology in human condition monitoring systems will simplify and accelerate this process, and most importantly, significantly reduce the cost of the equipment necessary for this procedure. Another field for applying our solution is bionic prosthetics, modern prostheses work using the myographic principle, the main disadvantages of which are expressed in high cost and in the long, requiring a significant number of invasive surgical procedures installation process, which is suitable not for all patients, due to health reasons, but also requires a lot of time for rehabilitation and adaptation to the management of the prosthesis.

#### **Scientific problem**

At the moment, to install a full-fledged bionic limb prosthesis, several invasive operations are necessary to prepare the patient for its use. General rehabilitation after surgery takes from several months to a year. The cost of a bionic prosthesis and associated operations for its installation is prohibitively high for the average patient.

At the same time, the bionic prosthesis cannot fully restore sufficient motor freedom to the patient, since it uses only one or two control chan-

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nels and allows you to only change the position of the upper limb and restores simple grasping functions.

The purpose and objectives of the study

Study objectives:

Development of technology to reduce the cost of installing a prosthesis.

And also the time for rehabilitation and mastery of patient management

1. To increase the number of control channels of the bionic system, thereby increasing its functionality.

Research objectives :

1. To conduct a study of brain activity associated with motor functions, and in particular the work of the precentral gyrus.

2. Selection of components and development of equipment for taking readings of activity of the precentral gyrus.

3. Software development for the interpretation of the EEG of the precentral gyrus.

Research methodology

Signal acquisition from the precentral gyrus, for use as a training sample, to create an artificial neural network, duplicating these readings with the readings of the restorative EMG restorative system for a more accurate classification of EEG signals.

Development of a new principle of interaction “Brain  $\Leftrightarrow$  Computer“, or rather, the transition to the system “Brain  $\Leftrightarrow$  Hypervisor  $\Leftrightarrow$  Computer“, where Hypervisor is an artificial neural network for interpreting data from the brain, in perspective and feedback between Computer  $\Leftrightarrow$  Brain.

Development of principles for interpreting signals of the precentral gyrus for the development of an artificial neural network of the hypervisor.

Research results, their interpretation and scientific significance

1. An activity map of the precentral gyrus of the brain with a training vector of the electromyogram of muscle activity.

2. The principle of using the hypervisor in the Brain system  $\Leftrightarrow$  Computer.

3. A trained artificial neural network for interpreting EEG signals from the precentral gyrus of the brain.

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### Practical application of research results

Further development and improvement of methods for classifying EEG signals, increasing the functionality of bionic systems, increasing the quality of life of patients with limited motor functions and further application of the presented systems in medical practice.

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## SYNTHESIS OF NANO-SIZED BISMUTH FRAMEWORK FOR BIOMEDICAL APPLICATIONS

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MOFs (metal organic frameworks) are porous structures, based on metal ions and organic linkers [1]. Compared to coordination polymers, they usually possess higher surface area and tunable pore volume. It should be noted, that for efficient drug delivery must be used only nano-sized MOFs (nano-MOFs), because they don't cause embolism and have better pharmacokinetic than micro-sized ones [2].

Bismuth is one of the least toxic heavy metals and due its excellent X-ray attenuation properties may be considered as the perspective CT agent. Combining high drug loading capacity of nano-MOF with CT contrasting properties of bismuth it is possible to make diagnostics and therapy of oncological diseases simultaneously. However, bismuth-based nano-MOF syntheses haven't been reported yet.

Here we suggest the method of nano-sized CAU-17 framework preparation by surfactant-modulated microwave synthesis. CAU-17 framework consists of Bi<sup>3+</sup> ions and trimesic acid and has a unit formula [Bi(BTC)(H<sub>2</sub>O)] [3]. MOF particles were characterized with DLS, SEM, EDS and Raman spectroscopy. Drug loading capacity and CT contrasting properties were also determined *in vitro*.

The further decreasing of CAU-17 particle size and investigation of its X-ray contrast *in vivo* have to be the next steps of this research.

The work was supported by Russian Science Foundation (Project 19-72-30012).

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## RAMAN SPECTROSCOPY FOR DIFFERENTIAL DIAGNOSIS OF THE BRAIN TUMOR

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Surgical removal of glial tumors is complicated due to infiltration of tumor cells into healthy brain tissue. Intraoperative navigation methods are widely used for their detection. Raman scattering (RS) spectroscopy allows detecting differences in the composition of the tissues in the absence of a fluorescent marker. In particular, the ratio of lipids to proteins in tumor cells is significantly different compared to normal cells.

**The target** of this work was to study the Raman scattering spectra of intracranial tumors of laboratory humans, respectively, in order to detect significant differences.

**Materials and Methods:** Studies were performed *ex vivo* samples of intracranial tumors of patients (glioblastomas and meningiomas). The raman spectra were obtained under irradiation at 785 nm.

**Results:** Significant lipid and cholesterol lines prevailed in the RS spectrum of normal brain tissue. In the tissues of intracranial tumors, the content of nucleic acids according to the Raman spectra was higher than in normal tissue. In addition, the glioma was characterized by a lower concentration of lipids compared with normal tissue and a higher concentration of nucleic acids and proteins, which can be explained by a less developed surface of the tumor cells membranes compared to normal cells and higher amount of cells participating in mitosis.

**Conclusions:** The results of the RS studies of the human intracranial tumors showed significant differences in the bands related to lipids, pro-

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teins and nucleic acids, which can be used for developing a method of  
brain tumor optical biopsy based on Raman spectroscopy.

*The study was carried out with the financial support of the Russian  
Foundation for Basic Research in the framework of the scientific project  
No 18-29-01062.*

**OPTICAL STUDIES OF A TWO-LAYER STRUCTURE OF  
ZNO / NANODIAMONDS (ZNO:DNDS)**

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The two-layer ZnO/DNDs structure provides a number of combined properties, including a large surface area, a defect-free interface, improved crystallinity, improved electrical properties and effective surface passivation, making these structures an ideal building block for optoelectronic applications. ZnO/DNDs dual-layer structures offer good performance in PD applications, field emission cathodes, and biosensors [1].

ZnO is a universal oxide semiconductor and has unique properties, such as a wide direct forbidden zone (3.37 eV) and a relatively large exciton binding power (60 eV at room temperature), which makes it promising for use in optoelectronics, including ultraviolet (UV) photo-detectors, field emission cathodes and solar cells.

The aim of this work was to analyze the optical properties of ZnO films doped with DNDs. The fluorescence spectra of ZnO films doped with DNDs at various concentrations and ZnO films without impurities and AFM images of these samples were obtained.

It should be noted that, in comparison with pure zinc oxide, DNDs additives increase its fluorescence by 5 times for the maximum DNDs concentration and lead to the formation of a shoulder in the region of 365 nm (fig. 1).

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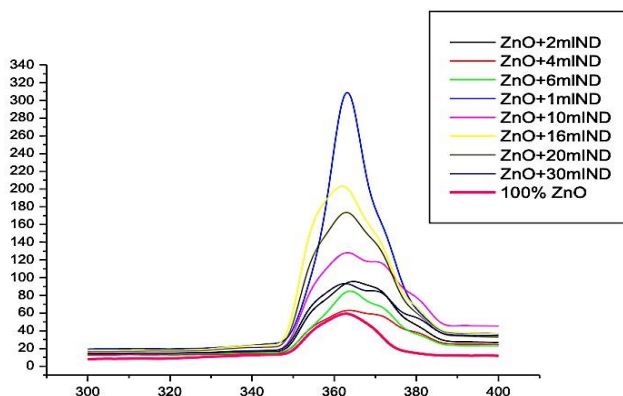


Figure 1. Fluorescence spectra of ZnO films doped with DNDs of various concentrations and ZnO films without impurities.

Thus, it was revealed that the presence of DNDs on the surface of ZnO films affects the optical properties of the material.

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**PROSPECTS FOR THE APPLICATION OF THE VALUES  
SUV<sub>MEAN</sub>, SUV<sub>PEAK</sub>, SUV<sub>MAX</sub> IN RADIONUCLIDE THERAPY OF  
DIFFERENTIATED THYROID CANCER 131-IODINE**

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**Relevance:**

Standardized uptake value of radiopharmaceutical (SUV) is one of the most perspective direction in nuclear medicine that focused on quantitative analysis using combined SPECT/CT systems.

Currently, annual growth of new cases of endocrine system diseases equals 4.5 % [1]. The most common are benign and malignant thyroid pathologies. Therefore, timely and evidence-based instrumental diagnostics is a necessary part of the medical care process.

There are countries such as South Korea, the USA, and Japan that actively apply SUV. This value has already proved its effectiveness in detecting malignant neoplasms such as: papillary, follicular forms of thyroid cancer [2-3].

**Purpose:**

Development of method segmentation image SPECT/CT and determination ablative range of reference values SUV<sub>mean</sub>/SUV<sub>peak</sub>/SUV<sub>max</sub> for different forms of thyroid tissue at post-therapeutic SPECT/CT during radioiodine therapy of differentiated thyroid cancer with 131-iodine.

**Materials and methods:**

SPECT/CT GE Discovery NM/CT 670 was used in this study. Software for segmentation of image - GE Medical Systems Xeleris 4.0 (Volumetrix MI) [4]. Segmentation was carried out according to a previously developed method, which is based on work with post-

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therapeutic SPECT/CT images with: attenuation correction, scatter correction, resolution recovery [5].

### **Results:**

Guidelines for segmentation of images SPECT/CT for radiologists and method of determination sensitivity was developed for SPECT/CT GE DISCOVERY NM/CT 670 during the study. The obtained data were used to plot dependency chart of  $SUV_{peak}/SUV_{mean}/SUV_{max}$  and the region of interest volume. According to the SUV frequency distribution, ablative reference intervals for the corresponding quantities were obtained.

### **Conclusion:**

The method of segmentation is applicable in semi-quantitative/quantitative object dosimetry and it's easily reproducible in the presence of a SPECT/CT workstation.

The obtained ablative reference intervals of values of  $SUV_{peak}/SUV_{mean}/SUV_{max}$  guarantee ablation effect for residual thyroid tissue during radioiodine therapy differential thyroid cancer with  $^{131}$ -iodine.

A preview protocol was developed for SUV implementation in differentiated thyroid cancer management.

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## AB INITIO MODELING BONDING ENERGY IN BIO-ACTIVE NANO COATINGS ON DENTAL IMPLANTS

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To minimize the implants fusion time with bone, special bioactive coatings are surfaced upon implants [1]. The most common biocompatible material for implants is titanium, one of the typical coating materials is hydroxyapatite (HAp)  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  (Fig. 1). Since cases of delamination at the implant-coating interface were observed in clinic [2], the actual problem is to study the adhesion strength of HAp with titanium. The characteristic of that strength is the binding energy between titanium and HAp. The purpose of this work was determination of the binding energy between the hydroxyapatite functional groups (anions) and Ti (II) titanium [3] with the help of computational quantum chemistry methods (computational chemistry suite Gaussian 09, Rev. C.01 [4]).

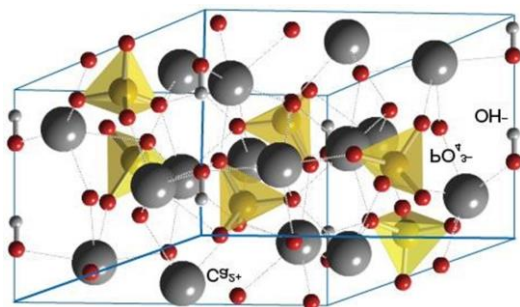










Fig.1. Hydroxyapatite (HAp)  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$

The study was carried out together with A. Balueva, P. Todebush C. Campbell, J. Magana, and N. Clement on the theme of the state assign-

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 ment (state registration number AAAA-A17-117021310386-3) and with  
 partial support of RFBR grants No. 17-08-01579 and No. 17-08-01312.

Table 1. Binding Energy of Ti(II) With Constituent Ions of Hydroxyapatite

	$\text{Ti}^{2+}$	$\text{OH}^-$	$[\text{TiOH}]^+$	$\text{Ti}(\text{OH})_2$	$\text{PO}_4^{3-}$	$[\text{TiPO}_4]^-$	$[\text{HO}_5\text{PTi}]^{-2}$	$[\text{H}_2\text{O}_6\text{PTi}]^{3-}$
Picture								
Ti-O Bond Lengths (Å)	N/A	N/A	1.8	1.73	N/A	1.94 per bond to Oxygen	1.82	1.87
Ti-O Bond Angles (degrees)	N/A	180	180	126	N/A	Approx. 74 per bond to Oxygen	81.4	78.0
Ground Energy of Structure (a.u.)	-844.42	-75.246	-920.4	-996.2	-638.2	-1484.5	-1559.9	-1635.2
Charge of Titanium	2+	N/A	1.124+	0.486	N/A	0.124+	-0.215	-0.888
Binding Energy (a.u.)	N/A	N/A	.734	1.28	N/A	1.88	2.03	2.09

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## REALISTIC NEUTRON SOURCE MODEL D-T GENERATOR FOR NEUTRON THERAPY

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Since the 1950s, the reaction  ${}^3_1\text{H}(d, n){}^4_2\text{He}$  has been used to obtain quasimonochromatic neutrons. Such generators are widely used to study the interaction of neutrons with reactor materials. They are also used in neutron activation analysis and neutron therapy. The wide resonance of the D-T reaction cross section in the neutron energy region of  $\sim 100$  keV allows one to obtain a large neutron yield when using low-voltage deuterium accelerators. It is often believed that such neutron sources are isotropic and monochromatic with an energy of 14.1 MeV.

A real source is neither isotropic nor monoenergetic. Primary neutrons are generated by deuterons that interact with the target material and their energy changes. Since radiation therapy places high demands on the accuracy of dose delivery, a careful specification of the source is required. Particular attention should be paid to the anisotropy of the neutron yield and their energy distribution.

To take into account deuteron beam deceleration during passage through a titanium-tritium target, it was divided into layers with a thickness  $\Delta x = 0.1$  mm. The change in the number of deuterons due to their elimination from the beam as a result of D-T reactions can be neglected. With a target density of  $\rho = 3.7$  g/cm<sup>3</sup> and an elemental composition of  $\text{TiT}_2$  the linear attenuation coefficient at the maximum of the D-T cross section of the reaction is  $\sim 0.4$  cm<sup>-1</sup>, and the range is about 2  $\mu\text{m}$ . The deuteron energy  $E_j$  at the entrance to the  $j$ -th layer was calculated

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as  $E_j = E_{j-1} - S_T(E_{j-1}) \times \Delta x$ , where  $S_T$  – stopping power of the target. Total number of neutrons  $N_j^n$ , formed in the  $j$ -th layer of the target, is determined by the energy of deuterons at the entrance to the  $j$ -th layer  $N_j^n = \frac{N^d}{S} \sigma_{DT}(E_j) \times n_T S \Delta x$ . Where  $n_T$  - concentration of tritium nuclei in the target,  $\sigma_{DT}(E_j)$  – cross-section. The probability of neutron emission at theta angle and its energy were calculated based on kinematic relations. The energy distribution was obtained by summing over all layers. Fig. 1 shows the energy (A) and angular distribution (B) of neutrons.

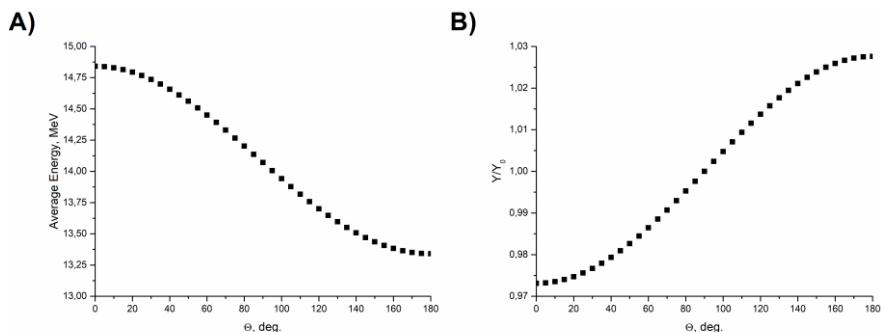


Fig.1. A) Angular distribution of the average kinetic energy of neutrons emitted from a thick target when it is irradiated with deuterons with a kinetic energy of 200 keV. B) Angular distribution of the neutron yield emitted from a thick target when it is irradiated with deuterons with a kinetic energy of 200 keV.

## **BIOLOGICAL EFFECTS OF SOLID RADIOACTIVE PARTICLES ON RATS**

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The radioactive particles production can occur when using "dirty bombs", nuclear explosions, as a result of radioactive emissions from nuclear industry facilities production of raw materials with high content of natural radionuclides, as well as nuclear and radiation accidents [1].

By now, much material much scientific matter has been accumulated on the protection of humans and animals from ionizing radiation [2], however, due attention is not paid to information about radiation injuries of the gastrointestinal tract. The aim of the study was to evaluate the biological effect on the internal parts of irradiating laboratory rodents (rats).

The study of the radioactive particulates biological action on laboratory rodents of both sexes, the rats of Wistar breed weighing from 200 to 300 g were used. In the experiments the silicate fused radioactive particles gage 80-160  $\mu\text{m}$  got by "uranium", "three-component" and "rhenium" models were used being approximately close to radiation characteristics of instantaneous fission products of about 10-15 hours age[3]. At the time of particles penetration into the animals body, their specific activity ranged from 3.7 to 7.4 GBk/g (100-200 MCi/g). Figure 1 shows the dependence of the activity and average energy of  $\beta$ -radiation on the time age of "uranium", "three-component" and "rhenium" model particles.

"Uranium" and "three-component" models are close to each other in the decline of activity in time. Beta radiation on average is not the same: the "uranium" model average beta radiation decreases over time from 0.65 to 0.35 MeV, and the "three - component" - increases from 0.53 to 0.87 MeV. "Rhenium" model differs from "uranium" in the terms of activity decline, but they are similar in changing of average energy of  $\beta$ -radiation in time.

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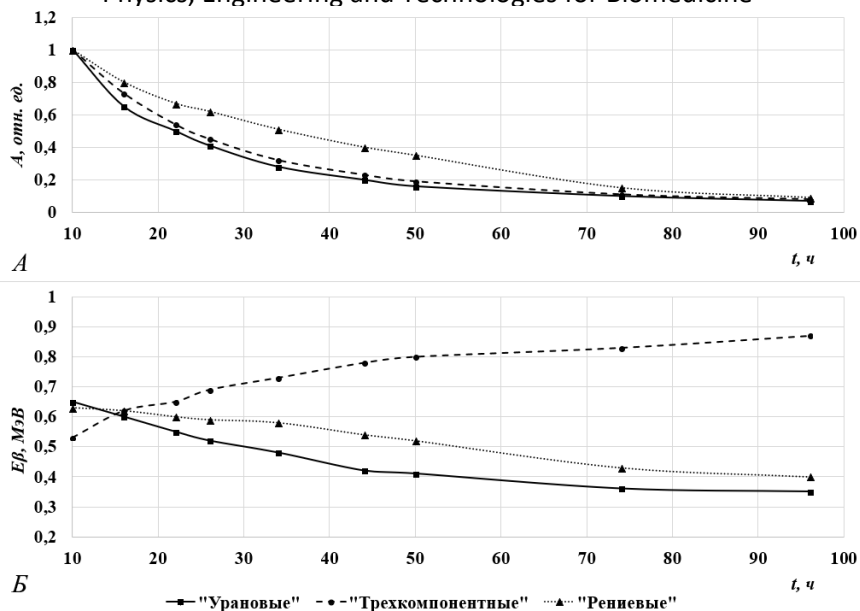


Fig. 1 Dependences on activity time and average energy of  $\beta$ -Radiation model of particles.

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## **DEVELOPMENT OF THE KNOWLEDGE BASE OF BREAST CANCER CYTOLOGICAL DIAGNOSIS**

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Currently, there is a significant increase in the number of oncological diseases such as stomach cancer, lung cancer, breast and thyroid cancer, etc.

The cytological method of research, in which the cellular composition of various human tissues and fluids is studied, helps to correctly and timely diagnose cancer. A cytologist with a light microscope detects the presence of cancer cells (or their absence).

Cytological research all over the world is used as a complete method of morphological verification of the diagnosis. The simplicity of obtaining the material, the preparation of preparations, the great potential capabilities of the method attract the attention of doctors of various specialties.

But even experienced specialists sometimes have objective difficulties: with rare or diagnostically complex tumors and tumor-like lesions; tumors, the clarification of the histological form of which requires additional diagnostic methods; border states; non-tumor lesions morphologically similar to tumors. Therefore, a cytologist, like any other doctor, must constantly study, replenishing theoretical knowledge and improving practical skills.

The availability of a sufficient database by a doctor would lead to a decrease in errors in the diagnosis and the selection of an adequate

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course of treatment. To date, such systems that can provide comprehensive support to a doctor are absent.

The purpose of the work is the development of an intelligent system for supporting the adoption of medical decisions in breast cancer.

To solve the problem, it is necessary to solve the following tasks of the project:

1. To form a set of signs for describing images of cytological gland preparations.

2. To select a sample of reference images of cytological images according to classical and problematic nosologies.

3. To develop a rating method for the support of medical decision-making

4. To form a model for processing diagnostic information in the decision support system.

5. To develop a model for the formation of a poor knowledge base of the decision support system.

6. To develop an algorithm for describing objects on cytological preparations of images of the mammary gland.

7. Implementation of the proposed solutions in the form of a software product (atlas directory to support the adoption of medical decisions)

8. Conducting experimental research

9. Development of techniques for working with the program and conducting descriptions to replenish the knowledge base.

The work is aimed at objectification of the morphological study of cytological preparations using artificial intelligence technologies.

The resulting system will make it possible to use it later in training medical students using high-tech diagnostic systems in continuing education of doctors from specialized and regional medical institutions.

## **IMPACT OF CHROMATIN SPATIAL ORGANIZATION ON DSB CLUSTERS FREQUENCY INDUCED BY LOW ENERGY IONS**

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When charged particle tracks penetrate a cell nucleus the most significant damage that occurs in the DNA owing to energy deposition are DNA single and double-strand breaks (SSBs and DSBs). A significant proportion of the initial energy of the charged particle is lost at the end of its path in the cell nucleus on a fairly short segment. For low energy ions linear energy transfer (LET) at the end of particle track reaches values much higher than in the initial part of the track at the cell or nucleus surface. This leads to much higher local energy deposition and results in more severe chromatin damage of increasing complexity.

To characterize severity of DNA/chromatin damage induced by low energy ions we simulated 3D stochastic structure of ion tracks and generated ensemble of chromatin structures with different spatial organization. Using polymer physics we modeled 3D structures of ~1 Mbp chromatin segment of different spatial organization: polymer globule and decondensed, looped conformations. By means of this technique we are able to assess simultaneously the impact of DNA topology and track structure with increasing LET on the incidence of clustered DNA DSBs within megabase-sized subunits of cellular chromatin. We simulated tracks of the following particles –  $\alpha$ -particles, nitrogen, carbon and oxygen ions with the following LET – 125, 267, 400, 648, 2128, 2200 keV/ $\mu$ m.

The numerical data reveal increasing the yield of clustered DSBs observed as yield of short DNA fragments as a function of ion's LET, see Fig.1.

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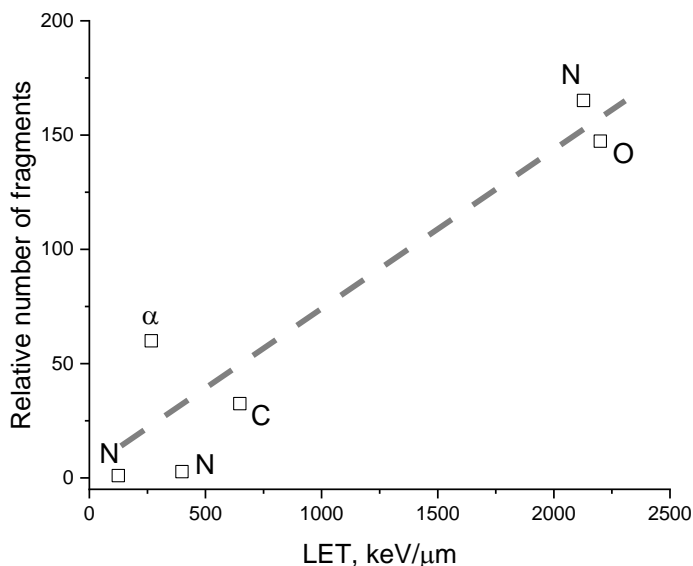


Fig.1. Relative incidence of DNA fragments (0.2 – 100 kbp) as a function of ion LET for N,  $\alpha$ , C, O ions. Irradiated structure: globular Mb-sized chromatin domain.

The calculations were performed per single energy deposition events in the chromatin. Data in Fig.1 are normalized on the yield of fragments for N ions with LET=125 keV/μm. The elevated yield of short DNA fragments with rise of LET is explained by increased track width with multiple intersections of the chromatin fiber within supramolecular 3D structure. Calculations for other chromatin structures indicate that the more decondensed is the structure, the gentler increase of DNA fragments yield with LET is observed.

**LOADING OF IODINE INTO PROMISING SILICON  
BASED CARRIER FOR DIAOGNOSTIC AND THERAPEUTIC  
BIOMEDICAL APPLICATIONS**

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Silicon (Si) nanoparticles (NPs) exhibit interesting physical properties, which are different for those of the bulk Si [1]. Biomedical applications of Si-NPs are stimulated by their low toxicity and biodegradability [2]. Si-NPs can be obtained by electrochemical etching [1,2] and laser ablation [3]. Radioactive iodine (<sup>131</sup>I) is widely used in radionuclide therapy for patients faced differentiated thyroid cancer [4], but there are several types of the thyroid cancer without selective iodine accumulation. Solid NPs can be used as containers for the <sup>131</sup>I delivery to the malignant non-differentiated thyroid tissue. Iodine loaded NPs can also act as a “marker” for the X-ray diagnostics of cancer.

In the present work we have explored iodine loading into porous Si-NPs by using tyrosine amino acid as a linker. Porous (P) Si-NPs were produced by electrochemical etching of crystalline silicon wafers in a hydrofluoric acid solution (HF 50%): C<sub>2</sub>H<sub>5</sub>OH (1: 1) for 1 h. Next, the films were dried and milled using a Fritsch Pulverisette 7 planetary mill to obtain powder and aqueous suspensions of PSi-NPs. The physical properties of PSi films and NPs were investigated by means the scanning electron microscopy (SEM), X-ray fluorescence (XRF), photoluminescence (PL) and dynamic light scattering (DLS).

It was observed a strong quenching of the PL intensity of microPSi layers and PSi-NPs after sorption of iodine molecules from ethanoic

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solutions. This effect is explained by interaction of negatively charged iodine-related centers with excitons in Si nanocrystals of PSi. The XRF analysis of iodine loaded PSi-NPs revealed characteristic peaks at 5.07 keV and 1.7 keV, which corresponded to iodine and Si, respectively. The iodine/Si ratio was found to be depended on pre-treatment of PSi.

Aqueous suspensions of PSi-NPs and those pre-treated by tyrosine solution were mixed with aqueous solutions of sodium iodine (NaI) to study the iodine sorption into pores of PSi. When the loading with iodine was done in acidic medium, which was controlled by adding of hydrochloric acid, the adsorbed iodine ions were detected in the prepared PSi NPs before and after centrifugation (see Table 1).

Table 1. Relative composition of iodine in the prepared samples of PSi NPs.

Treatment of PSi	$I_{\text{iodine}}/I_{\text{Si}}$	
	Tyrosine+NaI	HCl+Tyrosine+NaI
as prepared	0.36	1.63
after centrifugation	0	0.28

SEM and energy-dispersive X-ray (EDX) diagnostics indicated the binding of iodine ions to PSi-NPs. The EDX element maps showed that iodine ions were mainly bound to the surface of PSi-NPs with tyrosine coating in the presence of HCl. Thus, the acidic ambient is required to ensure significant binding of iodine ions to PSi-NPs. Further experiments are required to enhance the efficiency of iodine loading into PSi-NPs and to ensure the iodine binding stability for applications in the radionuclide therapy and X-ray diagnostics.

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## EVOLUTION OF THE PROPERTIES OF NANOMATERIALS OBTAINED BY PULSED LASER ABLATION

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The synthesis and application of metal and ceramic nanoparticle are significant subject in science and engineering. The metal nanoparticles such as gold, silver, and copper nanoparticles have more application in material science, nanomedicine, electronic, photonic, and art. One of the ‘green’ method for preparation of metal nanoparticles is laser ablation technique.

Colloidal solutions of plasmonic nanoparticles, such as gold and titanium nitride, have a number of unique properties, in particular, resonant absorption and scattering of light [1], as well as a huge amplification of the electromagnetic field near the surface [2], which makes them very effective both in catalysis [3] and in biomedical applications [4]. However, arbitrary transformations of the size, morphology and structure of nanoparticles during synthesis, and most importantly after its completion, during storage, temperature fluctuations and dilution of solutions is a significant problem. Uncontrolled and often unpredictable transformations lead to a loss of useful properties and a decrease in the reproducibility of the properties of nanoparticles, and hinder their practical application in biomedicine.

It should be noted that in laser ablation mechanism selection of parameters of laser radiation (wavelength, pulse duration, its power) allows you to finely control the process of formation of nanostructures, and therefore, allows you to obtain materials with the required characteristics [5].

Laser ablation of solids in liquids is an effective technique with considerable potential in the generation of nanocrystals, which allows mul-

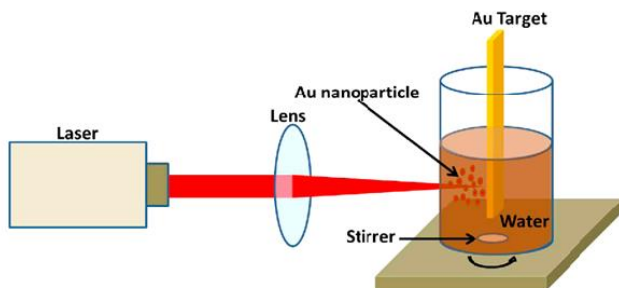
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 tilateral design through choosing appropriate solid target materials and  
 confining liquids [6].

In this work, gold colloids were prepared by pulsed laser ablation of  
 high purity gold plate immersed in deionized water and 10 $\mu$ M NaCl so-  
 lution.

Parameters of laser radiation:

Liquid	Energy,J	Laser WL,nm	Power,W	RR,Hz	Total Dura- tion,mins
Deionised water; 10 $\mu$ M NaCl	100 $\mu$	1030	1000m	10k	40 min; 30 min

In this communication, we study the change in the size distribu-  
 tion of nanoparticles after the ablation process over time. From the end  
 of ablation to the 21st day. Size distribution of obtained nanoparticles  
 was measured using dynamic light scattering (DLS) method. TEM im-  
 ages of nanoparticles were obtained at regular intervals after laser abla-  
 tion process.



Schematic diagram of the experimental setup of PLAL.

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## POLYLACTIC ACID FILMS IMPLANTATION INTO THE EYE IN VIVO

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Polylactic acid (PLA) is a biodegradable aliphatic non-toxic and eco-friendly polyester and is widely used as medical implants in the form of anchors, screws, plates, pins, rods, and as a mesh [1]. A comprehensive literature search reveals the applications of PLA and its polymeric composites in medical fields such as: orthopedics, drug carriers, facial fracture repair, tissue engineering, antimicrobial agents, antitumor, ureteral stents, biomaterials, miscellaneous applications [1]. Of particular interest is the use of PLA as a corneal implant for the bullous keratopathy treatment.

The purpose of this research is the study of the influence of thin polylactic acid films implantation on the corneal morphology *in vivo* experiment.

**Material and methods.** The feedstock for the films was obtained by dissolving polylactic acid (PURASORB® PL 10, Netherlands) in the chloroform (CHCl<sub>3</sub>). The surface topography was studied on “Centaur HR” (Russia). The surface roughness was estimated using the Gwyddion software. SEM of polylactic acid films was obtained by using Hitachi S3400N Type II microscope (Japan).

For *in vivo* experiment 8 pubescent female *Sylvilagus bachmani* rabbits (SSMU, Tomsk, Russia) weighing 2.0-2.5 kg were used. Polylactic acid films were implanted into the anterior chamber of one animal eye. The overall duration of the experiment comprised 21 days.

**Results.** The study of the structure and morphology of polylactic acid films showed that its roughness and topography depended on the side of the surface of the material: the outer side had a more embossed surface as opposed to a smoother inner surface. The surface roughness

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analysis showed that  $R_a$  of PLA films (inner) surface was  $0.01 \pm 0.003 \mu\text{m}$ ,  $R_q$  was  $0.014 \mu\text{m}$ ,  $R_{sk}$  was  $-0.001$ . PLA films (outer) surface had  $R_a = 0.17 \pm 0.06 \mu\text{m}$ ,  $R_q = 0.4 \mu\text{m}$ ,  $R_{sk} = -1.0$ .

The implantation of the PLA film did not cause an inflammatory reaction and did not increase an intraocular pressure.

The following histological results were obtained. The anterior epithelium was represented by 4-5 layers of squamous epithelium with normochromic nuclei. Bowman's membrane was unchanged and visualized as a homogeneous eosinophilic strip. Collagen fibers were located compactly. In some places collagen fibers had increased twisted stroke. Descemet's membrane was visualized throughout. The endothelial layer was represented by a single layer of cells. In some places proliferation of endothelial cells in the form of process cells was observed.

**Conclusion.** The implantation of the PLA films into the anterior chamber of eye does not induce an inflammatory reaction and does not increase an intraocular pressure. The study showed the possibility of PLA films using as a corneal implant.

**Acknowledgments.** The research was conducted with the financial support of the Russian Foundation for Basic Research (RFBR) as part of the project № 19-415-703005.

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**SIMULATION BY FEM OF THE OPTOACOUSTIC EFFECT  
PRIOR TO TREATMENT BY PHOTODYNAMIC THERAPY  
FOR CANCER PATIENTS**

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The optocoustic effect that is generated when a laser interacts with a structure is simulated qualitatively and quantitatively by in silico tests to describe the physical quantities obtained from the interaction of a pulsed laser with a medium [1]. These physical quantities were calculated and compared with the simulation. The working interface of the ANSYS software allows to model and attribute controllable properties to simple and complex structures allowing the analysis of different materials with approximations to the properties of biological structures. Additionally, these in silico tests allowed us to understand the dynamics of the physical principles of the optoacoustic effect, such as the variation of temperature, pressure and intensity of the laser and the dynamic-qualitative description of the particle wave duality of light, physical phenomena of transmission, reflection, dispersion, absorption, depending on the properties of the medium with which the radiation interacts. An overview of the rapidly expanding field of photoacoustic imaging for biomedical applications and cancer detection is provided.

Different ANSYS tools were used to analyze the temperature, pressure and intensity of the laser interaction individually. Water was established as aqueous medium contained in a cuvette of negligible optical properties, a laser light source at 1064 nm wavelength, with a pulse time of 10 ns, energy per pulse of 20  $\mu\text{J}$  (E0) and a radiation area of 1 mm (rspot). From these simulations have been obtained thermal confinement results in the order of  $6.699 \times 10^{-3} \text{ }^{\circ}\text{C}$  that is generated in a measure of

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pressure in the medium with measurable magnitude in the range of  $5.606 \times 10^{-3} \text{ Pa}$  [2].

This technique is an alternative in detection systems of cancer cells, enzymes, physiological parameters, biomarkers, chromophores, oxygen concentration and saturation of hemoglobin and gene expression products allowing to obtain biomedical images. This technique in detection systems has a high temporal resolution, constitutes a low cost non-invasive method where ionizing radiation is not used and it does not generate side effects. Optical imaging has a nanomolar-level of sensitivity, parallel to nuclear methods such as PET and SPECT, and has the capability to detect over a dozen different molecular species [3,4]. Given that it constitutes a method with high sensitivity and specificity, the study and analysis of this by *in silico* tests determines its importance prior to any type of *in vivo* treatment.

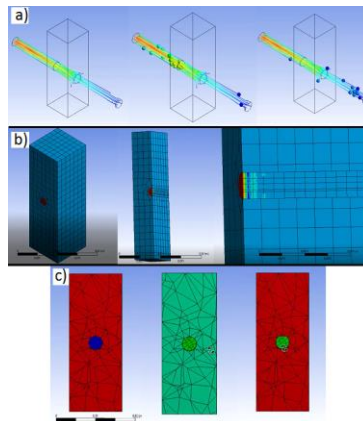


Fig.1. Experimental scheme of a dye laser with semiconductor pumping

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**EFFECT OF ELECTROLYTE CONDUCTIVITY, SIZE AND  
SURFACE CHARGE OF DISPERSED NANOPARTICLES ON  
HEAT RELEASE IN RADIOFREQUENCY ELECTRIC FIELD**

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Currently, there is a need for new methods for cancer therapy. One of these methods is based on local hyperthermia (HT) because of heating of nanoparticles (NPs) localized in cancer cells and tumors. While ferromagnetic or superparamagnetic NPs heated by alternating magnetic field are usually explored in magnetic HT [1], the residual toxicity of those NPs is a limiting factor for their clinical applications. As an alternative to the magnetic HT it was proposed to use nontoxic silicon (Si) NPs, which act as sensitizers of radiofrequency (RF) electromagnetic HT because of the Joule heating related to local electric currents around NPs [2].

We analyze spherical NPs with radius  $a$  in an electrolyte with various electrical conductivity under irradiation with RF electric field  $E(t) = E_0 \cos \omega t$ . Considering the electric field distribution nearby the NP, which is determined by solving the corresponding Poisson's equation, the mean rate of heat release around the NP can be calculated as follows:

$$Q_{out} = \frac{\pi}{qT} \int_0^T \int_a^L \int_0^\pi E_{out}^2(t, r, \theta) \frac{\Omega \omega^2}{\Omega^2 + \omega^2} \sin(\theta) r^2 dr d\theta dt, \quad (1)$$

where  $T = 2\pi/\omega$  is the period of the RF electric field oscillations,  $\sigma$  is the specific electrical conductivity and  $\epsilon$  is the permittivity of electro-

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lyte,  $\Omega = \frac{\sigma}{\varepsilon \varepsilon_0}$  is the reciprocal Maxwell relaxation time,  $L$  is the characteristic dimension of the thermal fields overlapping from neighboring NPs, and  $q$  is the elemental electrical charge. The total heating rate can be obtained by multiplication of  $Q_{out}$  on the NP concentration and the contribution of NPs into the heating is obtained by subtracting the heating rate of the homogeneous electrolyte of the same electrical conductivity.

Fig. 1 shows calculation results and experimentally determined heating rate for RF-irradiation of aqueous electrolytes with dispersed Si-NPs versus the specific electrical conductivity of the electrolyte.

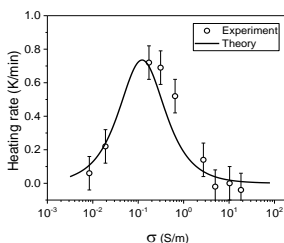


Fig.1. Dependence of the heating rate of aqueous suspension of Si-NPs with mean size of 15 nm and concentration of 1 g/L under RF irradiation at 27 MHz with mean power 10 W versus the specific electrical conductivity of electrolyte adjusted by adding of small amount of hydrochloric acid. Open circles and solid line represent the experimental data and their fitting by using Eq.(1).

The proposed model allows us to explain the observed nonmonotonic dependence of the RF-heating rate on the electrolyte conductivity and it can be useful for choosing the optimal parameters of NPs and RF-radiation for applications in hyperthermia of malignant tumors.

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## METAL-ORGANIC FRAMEWORKS FOR MRI

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It is impossible today to imagine modern clinical evaluation in cardiology, oncology, and many other realms of healthcare without magnetic-resonance imaging. Over the past decade, the application of MRI has increased, due to its ability to generate sharp images without resorting to ionizing radiation. MRI is known for its high resolution, sensitivity and specificity. However, the presence of artifacts at MR imaging can obscure relevant anatomy and disease.

An artifact of MRI is a false intensity of signal on the image which does not correspond to parameters of an evaluated tissue. It should be noted that almost any MR image has artifacts.

Artifacts appear in MRI for a variety of reasons. Potential sources of artifacts include biological behavior and intrinsic tissue properties like presence of air microbubbles, ferritin deposition, etc. Presence of artifacts decreases diagnostic possibilities of MRI, making accurate data interpretation more difficult.

This problem can be solved by using smart contrast agents [1]. Here we propose to use metal-organic frameworks of the MIL family based on Fe<sup>3+</sup> ions [2] for that purpose. We can specifically detect signal only from Fe-MIL-101\_NH2 nanoparticles due to its rapid change of MR contrasting properties from T1 to T2 during frameworks degradation in the presence of phosphate-ions. We suggested to use nanoparticles with surface modification by covering with a layer of SiO<sub>2</sub> [3] to control their rate of degradation. The particles were studied by dynamic light scattering, Raman spectroscopy, and scanning electron microscopy.

The work was supported by Russian Science Foundation (Project 19-72-30012).

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## **BiOCl NANOPLATES AS X-RAY CONTRAST AGENTS**

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A wide variety of nanoparticles (NPs) are used currently in biomedicine. One of the perspective directions is creating X-ray contrast nanoagents for computer tomography (CT) investigations. Bismuth NPs can significantly improve CT-diagnostics because Bi have the largest X-ray absorption cross-section among non-radioactive materials and low toxicity for the organism. Here, we synthesized BiOCl nanoplates and investigate their properties as peroral CT-agent.

For NPs synthesis  $\text{BiCl}_3$  was hydrolyzed in NaOH until white precipitate of nanoparticles was formed. Then, NPs were stabilized by coating with citric acid. The smallest fraction of NPs was separated by centrifugation in sucrose gradient. Reaction yield was 88%.

Obtained NPs were characterized with SEM, DLS, EDS and different spectroscopy methods. SEM shown, that NPs have a form of nanoplates with 120 nm length and 20 nm thickness. Hydrodynamic size in distilled water also was 120 nm, NPs have negative  $\zeta$ -potential. Summary data from RAMAN, FTIR, UV-VIS spectroscopies and EDS analysis shown that material have BiOCl composition without significant impurities.

To investigate particle stability in gastric and intestine conditions, we incubated them in simulated fluids (0.1 M HCl – for stomach, 6.8 pH PBS – for intestine) for 1 day. We didn't observe any signs of bismuth ions leakage by ICP-mass spectroscopy measurements.

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X-ray contrast properties of BiOCl nanoplates were tested *in vitro* and *in vivo*, in comparison with classic peroral CT-agent: BaSO<sub>4</sub> meal. *In vitro* NPs shown 2 times brighter signal then BaSO<sub>4</sub>. Also, BiOCl NPs allow us to clearly visualize stomach and small intestine loops even at low voltage X-Ray investigation.

We believe, BiOCl nanoplates can be used in future as non-toxic and bright X-ray contrast agent for CT-diagnostics of various pathologies of gastro-intestinal tract.

The work was supported by Russian Science Foundation (Project 19-72-30012).

**PHYSICAL PROPERTIES AND POTENTIAL BIOMEDICAL  
APPLICATIONS OF SILICON NANOPARTICLES WITH IRON  
IMPURITIES**

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Silicon (Si) nanoparticles (NPs) are promising for biomedical application due to the fact that they have low toxicity and can be eliminated from the body by biodegradation into orthosilicic acid [1]. It was shown that Si based NPs can be used in cancer therapy as drug carriers, sensitizers of ultrasound and high frequency electromagnetic radiation [2-4]. Control of the NPs accumulation in the tumor after intravenous administration is crucial for the effectiveness of therapy. The best results can be achieved when the NPs can be controlled and simultaneously used in therapy.

Diagnosis and treatment monitoring of internal human cancers by current available methods involve the use of monitoring systems based on magnetic resonance imaging (MRI) technique. The method is excellent for diagnosis of primary and metastatic lesions and for monitoring in subsequent follow-up of cancer therapy.

Si-based NPs with 0.2, 2.5, 5 and 10 atomic % of iron (Fe) were prepared by arc-discharge plasma-assisted ablative synthesis from poly-

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crystalline Si powder mixed with metallic iron powder and then were used to prepare stable aqueous suspensions. The physical properties of the prepared NPs were investigated by means of the electron microscopy, X-ray diffraction, Mossbauer spectroscopy, Raman scattering, dynamic light scattering and magnetic properties measurements.

Both the transverse proton relaxation time and longitudinal one decrease strongly in the prepared suspensions due to a high density of the electron spin centers in NPs and iron impurities. The maximal transverse proton relaxivity was around 10 L/(g·s). Aqueous suspensions of NPs at concentrations above 0.1 g/L exhibit noticeable contrast enhancement for the T2-weighted MRI.

In-vivo MRI visualization of mice with grafted malignant tumor and intravenously administrated NPs revealed darkening of the tumor area in T2-weighted images, which indicates the accumulation of nanoparticles in the tumor. The obtained results show possibility of using Si NPs with iron impurities in biomedicine.

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## **PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING OF CERIUM OXIDE NANOPARTICLES**

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Recently, interest in the field of nanomedicine has been steadily growing. Cerium oxide nanoparticles are one of the promising materials in this field due to their ability to interact with reactive oxygen species (ROS) and perform the functions of enzymes. It was shown that these nanoparticles are able to protect cells from ROS and prevent diseases associated with oxidative stress in the body [1]. However, the further development of their biomedical applications, for example, the design of drugs based on CeO<sub>2</sub> nanoparticles, is difficult due to the deficiency of necessary information about the toxicity and distribution of nanoparticles in the body.

A physiologically based pharmacokinetic modeling (PBPK) is a useful tool for predicting the absorption, distribution, metabolism and excretion of nanoparticles, as well as evaluation their toxicity under various conditions [2]. Therefore, the aim of this work was to develop a physiologically based model of pharmacokinetics for intravenously injected cerium oxide nanoparticles.

Simulations were performed using Matlab SimBiology<sup>®</sup> R2018b software. The model was optimized using derivative-based method.

The pharmacokinetics model includes ten compartments, each of which describes the nanoparticles behavior in a certain organ. The model consists of lungs, spleen, liver, kidneys, heart, brain, gastrointestinal tract, other organs, as well as arterial blood and venous blood. Each compartment contains three subcompartments: capillary blood, tissue, and phagocytes. Like biological systems, all compartments in the PBPK model are linked to each other by the circulating blood system.

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The biokinetics of nanoparticles within each compartment was described using a series of linked ordinary differential equations.

The model was optimized based on the known experimental data on the distribution of CeO<sub>2</sub> nanoparticles in various organs of rats (for example, [2]). The model parameters characterizing the physiological and anatomical properties of the object, as well as the physicochemical properties of the nanoparticles, were taken from the literature sources [3]. The remaining parameters with unknown values were optimized by fitting the model parameters and comparing the model results with experimental data. In order to simplify the model, the parameters had the same values for most organs.

The sensitivity analysis of the model was carried out to determine the parameters that have the greatest effect on the nanoparticles biokinetics. It was found that the pharmacokinetics of nanoparticles is more dependent on the distribution coefficient between tissue and blood, the permeability coefficient between blood and tissue, and the maximum rate of phagocyte uptake. Thus, it was shown that both the anatomical and physiological parameters of rats, as well as the physicochemical parameters of nanoparticles, influence the biodistribution of nanoparticles.

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**NUCLEIC ACIDS WITH MODIFIED BACKBONE:  
A THEORETICAL STUDY**

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Xeno Nucleic Acids (XNAs) are a group of chemically modified nucleic acid analogues with altered properties compared to natural DNA/RNA that are widely used in biological and medical applications [1,2]. Furthermore, XNAs are important for investigating the chemical etiology behind why nature chose ribofuranosyl nucleic acids over other possible nucleic acid chemistries [3,4]. There are two main directions of changing the structure of nucleic acids: modifications of the backbone or nucleic bases. Both of them are exploited in drug discovery. For example, oligomers containing modified nucleotides are considered as a drug in antisense oligonucleotide therapy and as a source of sequences in aptamer selection. Artificial nucleic acids have a lot of advantages over biological nucleic acids: the modified backbone can be charge-neutral facilitating cellular uptake; some of XNA molecules form more stable hybrid complexes with biological oligomers and molecules with modified phosphate moiety are less vulnerable to cleavage by nucleases.

Despite tremendous advances in the experimental synthesis of xeno-nucleic acids, there is a lack of theoretical knowledge about a relationship between the structure of backbone and mechanical and structural properties of resulting double-helix. To pave the way for understanding this relationship we conducted a series of all-atom molecular dynamics simulations of novel xeno-nucleic acids with different backbones. We considered double helices consisting of nucleic acids with backbone based on two types of flexible chains (polyethylene and organosilicon) with different monomer size (Fig. 1). First of all, we found out that molecules with such backbones form stable double-helical structures under temperature of 300 K. Also, increasing the size of monomer widens

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double-helix. While the energy of base-pair hydrogen bonds is almost unaffected by the structure of backbone, stacking interaction is more constrained in case of short monomers. Presented results have the potential for application in the rational design of novel xeno-nucleic acids.

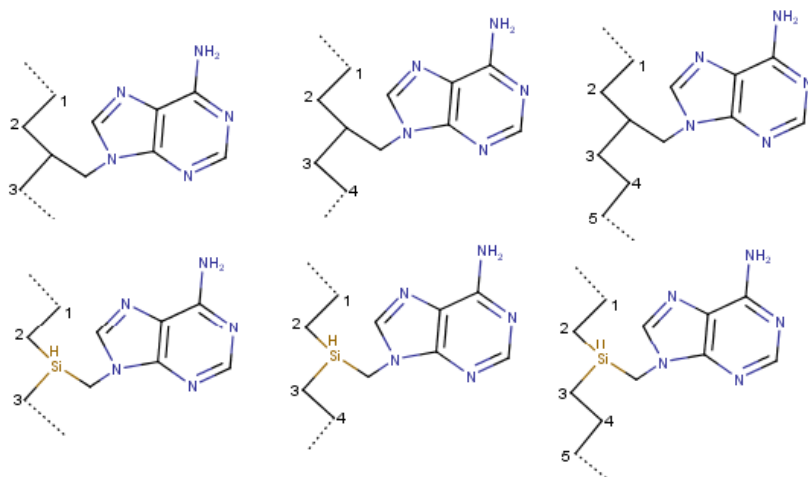


Fig. 1. Structures of nucleotides with modified backbone studied in this work (only adenine is shown as an example)

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**DEVELOPMENT OF MODELS OF ANALYSIS OF  
STRUCTURAL ELEMENTS ON IMAGES OF SKIN  
MELANOMA**

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A promising direction for the use of artificial intelligence systems for the diagnosis of skin melanoma is the study of machine learning algorithms, whose capabilities have not been previously evaluated in similar works. The aim of work is creation of a system designed for the study of artificial intelligence algorithms in the task of automated diagnosis of melanoma.

The initial step in creating a system for automated recognition of medical images is to search for images of organs or tissues with a diagnosis. These may be images provided by medical institutions, but samples in such cases often do not have the required representativeness. In view of this, you can use existing image repositories. Their plus is that they accumulate medical images in themselves specifically for solving the recognition problem. In this case, we will consider some dermatoscopic atlases with examples of diagnosed melanomas (“malignant”) and cases where the diagnosis was not confirmed by subsequent studies (“benign”).

With the help of digital processing of dermoscopic images, knowledge bases, expert systems, medical decision support systems, a significant increase in diagnostic accuracy can be obtained, since only digital image processing can give quantitative characteristics for the objective classification of images by type of neoplasm.

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Many modern dermoscopic algorithms (modified pattern analysis, “Chaos and Signs”) are based on the number, location and description of neoplasm elements, such as “lines”, “pseudopodia”, “circles”, “lumps”, “points”, etc. Therefore, the selection and description of areas of the element of pigmented skin neoplasm is an important step in the framework of the program implementation of dermoscopic algorithms and the construction of an automated diagnostic system for skin neoplasms.

During the implementation of structural element analysis models, a segmentation map is built — an image in which the pixel brightness is equal to the segment identifier. Thus, having received the coordinates of all segments, it becomes possible to calculate the area of the segments in pixels. If the area of any segment is less than the specified value, then on the segmentation map, all pixels adjacent to this segment (boundary pixels) are searched. Among the found pixels, the class segment of the majority is determined, to which this segment joins.

Based on the obtained map of segments, an analysis is carried out and structural elements are selected to assess the malignancy of the neoplasm.

The work was supported by the RSF project № 19-11-00176.

## **MODERN METHODS OF DONOR ORGANS PRESERVATION DURING REMOTE TRANSPLANTATION**

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Currently, the shortage of donor organs problem has acquired a new, non-classical form. On the one hand, the success of health care is such that many diseases that previously required transplantation of the affected organ can now be treated medicamentally, often in the early stages of the disease. So there are fewer potential recipients (and there should be more "free" donor organs). But, on the other hand, the same people now cured by modern medicine previously could become postmortem donors of their healthy organs (in case of unsuccessful treatment). So there are fewer potential donors too. Thus these two features somehow balance each other.

The "discovery" of previously unavailable for high-tech medicine regions of the country also suggests an increase in the number of potential donors and recipients. The ubiquity of transport (public and personal) and the concomitant increase in the number of accidents accompanied by injuries to vital organs (potential recipients) or fatal outcomes (potential postmortem donors) lead to the same result. According to the International Registry of Organ Donation and Transplantation in the 6 years period (since 2012) the deficit of donor organs in Russia has increased by 4.7 % (table 1).

An essential problem with transplantation, both in the past and now is the inefficient use of even those scarce donor organs that are available [1]. This is primarily due to:

- Impossibility of the correct selection of a suitable "donor-recipient" pair
- Biological death of a donor organ on the way to a potential recipient.

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Table 1. Statistical information on the number of organ donors in Russia

Donors\Year	2017	2016	2014	2012	2010
Postmortem	516	432	359	291	281
Multiorgan	375	312	235	195	174
Relative	332	381	316	299	256
Effective	564	487	465	412	487

The first problem is caused by the applied methods of preservation [2], which do not allow all the necessary analyzes of the donor organ to be carried out. The second one is an acute lack of time, although some organs can last in vitro for only a few hours (e.g. liver).

The solution to both problems can be the creation and implementation in clinical practice of systems that ensure the preservation of donor organs for a long time using mechanical perfusion methods. Such systems have a number of advantages that make transportation and subsequent transplantation more effective, which helps to save scarce donor organs:

- Donor organs connected to the perfusion system are stored for several days
- All the necessary tests can be carried out due to zero cooling.

An example of such system is Organ Ox Metro support system developed at Oxford University. It implements the functions of auxiliary circulation and blood oxygenation. It is assumed that the system will be able to support the donor lungs, heart and liver. The system is currently undergoing clinical trials at the Royal medical hospital of Oxford University.

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**A PROPOSED MECHANISM OF DEVELOPMENT  
CONTROL OF THE SERVICE OF RADIODIAGNOSIS**

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Described existing problems is not an efficient use of resources and diagnostic units. Identified three objectives to address them: the modernization of the regulatory framework of the service of radiodiagnosis, optimization of the education of specialists in radiation diagnosis, classification of managerial decisions on the level of medical organizations. Shows the activities for implementation of these tasks.

To solve the first problem it is necessary:

1)conduct the timing of diagnostic studies on various types of modern equipment by different vendors, and organize this data for a more rational use of equipment;

2)to determine the order of interaction between structural units of the service of radiodiagnosis and interoperability specialists;

3)introduce the concept of “diagnostic complete case” Completed case treatment in hospital - a set of diagnostic health services in accordance with the standard of medical care for major diseases provided by the patient on a schedule date in the form of diagnostic medical aid, confirmed by the original medical records.

These regulations consolidate the law.

To solve the second problem it is necessary at the state level to change existing educational system:

1)increase the number of hours of educational programs on to the diploma stage to 200;

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2)in all clinical disciplines within higher education to study carefully all radiation semiotics of diseases with the development of practical skills;

3)to introduce a comprehensive clinical residency, after which award the qualification doctor of radiation diagnosis with the competences of classical radiology, ultrasound diagnostics, CT, MRI;

4)it is necessary to implement the new unified program that takes into account all the new “revolutionary” technology;

5)require all clinical specialists to receive professional training in x-ray diagnostics in the framework of their professional competence;

6)effectively used to improve the training of specialists of the system of continuous medical education.

To solve the third problem managers of healthcare organizations to optimize the activities of the service of radiodiagnosis to use the principles of LEAN management, in the framework of existing legislation to motivate staff to develop new research methods, conduct personnel rotation within the units.

The proposed activities under this project approach:

- 1)reduce the financial and time costs of preparation of specialists;
- 2)improve the quality of services;
- 3)enhance the rational use of equipment.

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**CT AND HISTOLOGICAL SIGNS OF MUCINOUS  
ADENOCARCINOMA OF THE STOMACH**

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With the help of computer tomography (CT) and histological methods to demonstrate features of histological types of cancer of the stomach - mucinous adenocarcinoma (synonyms: mucoid, colloid, gelatinosis cancer) and tumor response to preoperative chemotherapy (NCT) and chemoradiotherapy (NCRT).

Describes two cases of mucinous cancer of the stomach in the process of neoadjuvant therapy: clinical observation №1 – the patient received preoperative chemotherapy, clinical case №2 - the patient at the preoperative stage was conducted chemoradiation therapy. The patients underwent multislice computed tomography (MSCT) before treatment and 2 months after its completion. We compare data initial and control CT to analyze the changes of symptoms of neoplastic lesions, structure, size, densitometric density of the tumor and regional lymph nodes lymph nodes. Preparation of material for histological examination was carried out according to standard protocols. To assess the therapeutic pathomorphosis used a four-level system of evaluation of tumor response was proposed by the Japanese research society of gastric cancer, in both cases, therapeutic pathomorphosis of 3 degrees.  
Clinical case №1.

Slime poorly-differentiated adenocarcinoma with signet ring cell component body, and cardia of the stomach, pT2N2M0G3. CT studies before and after preoperative therapy, the tumor was characterized by irregular, indistinct contours due to infiltration parasternal fiber, its structure is heterogeneous with areas of decreased density in the treat-

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ment process, the number of hypodense areas had increased. These areas correspond to “lakes” of mucus, which was confirmed by histological examination of surgical material.

Clinical observation №2.

Slime poorly-differentiated adenocarcinoma of the gastric cardia, pT4aN2M0. CT before and after preoperative therapy of a tumor with uneven, sharp contours, its structure is heterogeneous with extensive circumscribed areas of decreased density in the treatment process, hypodense areas were consolidated with the formation of clear hipertensao delimiting their contour, due to the fibrous tissue. These areas correspond to “lakes” of mucus, which was confirmed by histological examination of surgical material. The decline in quantitative CT of the symptoms and the appearance of fibrous loop, and Association “lakes” of mucus can be explained by the effects of radiation therapy.

These clinical cases demonstrate CT and histology of mucous cancer, as well as features of the response of the tumor to preoperative treatment. It is shown that under the influence of chemotherapy increases the production of mucus by the tumor, while radiotherapy is the consolidation of a mucous component with the formation of extensive lakes and marked fibrosis separating them.

Isolated application of methods of diagnostic imaging does not cover the entire depth of the changes of the tumor in the process of pre-treatment, in particular a CT scan allows us to see its entire scope, to assess the macrostructure, to determine the involvement of neighboring anatomical structures and regions. Histological method, by contrast, shows the changes of the microstructure of the tumor, the number of remaining “live” tumor cells, the presence of fibrosis in the parenchyma.

Thus, the use of an integrated diagnostic approach clinical (CT) and histological gives you the opportunity to compare these data, to see the full picture of tumor response to therapy and to predict the course of the disease [1].

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**HISTOLOGICAL AND CT DIAGNOSTIC METHODS IN THE  
EVALUATION OF TUMOR RESPONSE TO CHEMOTHERAPY  
AND CHEMORADIO THERAPY IN PATIENTS WITH  
LOCALLY ADVANCED GASTRIC CANCER**

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Gastric cancer is a problematic disease, despite the introduction of new treatment regimens. Therefore, still deals with selecting the optimal extent of surgery and efficacy of neoadjuvant and adjuvant treatment. Given that the objective assessment of tumor response to the proposed treatment plan – definition of therapeutic pathomorphism, which was only possible after the surgery, an urgent task is the development and implementation of objective criteria for the evaluation of tumor changes in patients with gastric cancer at the preoperative stage. At the moment, one of the leading methods of evaluating changes of the tumor in the combined treatment process is computed tomography (CT). Thus the aim of this work was comparison of the CT symptoms of tumor response and histological pattern in patients with locally common form of stomach cancer receiving different types of neoadjuvant therapy to assess the most effective method of preoperative effects.

We analyzed the results of CT examinations of 103 patients with histologically verified diagnosis of gastric cancer (T0-4bN0-3aM0) before and after treatment: 41 patients treated with preoperative chemoradiotherapy (NCRT) and 62 patients who received preoperative chemotherapy (NCT).

To determine the degree of therapeutic pathomorphosis of surgical material used the system of the Japanese society for the study of gastric cancer. The distribution of the patients are shown in table 1.

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Held a vintage analysis of the CT symptoms and findings of therapeutic pathomorphism.

Table 1. Histological characteristics of patients

Treatment	All patients	The degree of pathomorphosis					
		1a-1b		2		3	
		abs.	%	abs.	%	abs.	%
NCT	62	-	-	19	30,6	43	69,4
NCRT	41	15	36,6	3	7,3	23	56,1

Revealed that therapeutic pathomorphosis 1a and 1b of degrees was found only in the group of patients treated with preoperative chemoradiotherapy. Pathognomonic symptom for these degrees has been the emergence of similarity “stratification”. According to the received data, statistically significantly differed in the dynamics of densitometric density of the tumor in the native and the arterial phase of contrast enhancement in the process of neoadjuvant therapy in patients depending on the degree of pathomorphosis. In native phase among patients with 1a-1b with the degree of pathomorphosis of the tumor density decreased, on average, 22% with grade 2 in 17%, and in patients with 3 degree of variability remained at approximately the same level (increased by 0.2%). Similarly was characterized by a change of the densitometric density of the tumor in the arterial phase in patients with 1a-1b degree of variability, the average was reduced by 31%, from 2 degrees to 7%, and in patients with 3 degree of variability of 2%.

Therefore, a comprehensive multidisciplinary diagnostic assessment of tumor response, in particular, histological examination, immunohistochemical and molecular status, radiation data visualization, and their comparison can give a more precise answer about the effectiveness of the treatment used [1,2,3].

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## **MUSCLE RESPONSE REGISTRATION DEVICE FOR DIAGNOSTIC OF NEURODEGENERATIVE DISEASES**

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Neurodegenerative diseases are characterized by slowly progressing death of neurons and gradually increasing atrophy of the corresponding parts of the brain and (or) spinal cord. One of the main signs of neurodegenerative diseases is motor dysfunction, which leads to a decrease in the patient's ability to move and serve himself. This fact indicates the important social significance of the problem of such diseases [1].

The study of nerve conduction is an informative diagnostic assessment method in determining the degree of muscle damage in neurodegenerative diseases, which shows the relevance of this work.

Evaluation of muscle responses to peripheral nerve stimulation can be performed by the following methods: according to clinical signs, instrumental evaluation methods (tactile evaluation, electromyography, accelerometry, mechanomyography) [2].

The developed monitor allows you to evaluate the response of the affected muscle in neurodegenerative diseases to stimulation of the peripheral nerve and calculate the blockade of neuromuscular conduction. The device is based on the electromyography method, which was not used in serial domestic analogues. The advantage of the method is the availability of application for a wide range of patients both for the purpose of diagnosing the early stages of diseases and identifying risk groups at the preclinical stage, and the ability to assess the condition of patients with an already developing disease. This fact shows the practical significance of the work.

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A block diagram has been developed. It is shown in Figure 1.

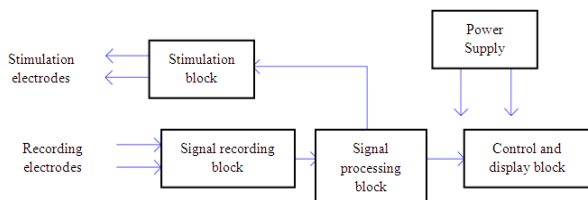


Fig. 1. Generalized block diagram of the device

On the basis of the structural scheme, a principal was developed.

To enable further analysis of the received muscle responses, it is possible to transfer data to a personal computer.

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## STUDY OF CIRCUIT SOLUTION FOR A COMPUTER ELECTROENCEPHALOGRAPHY MODULE

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In the course of this work, an eight-channel module for recording an electroencephalogram of a person was developed. The analysis of options for constructing structural schemes for recording the brain's biopotentials is performed.

An electroencephalograph is a device consisting of a number of electrodes that record the difference in biopotentials taken from the head[1]. The block diagram of the EEG module is shown in Figure 1.

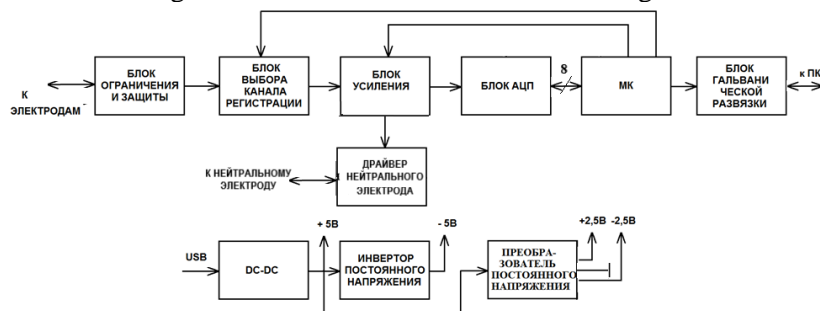


Figure 1 - Block diagram of a computer electroencephalograph

The developed module contains 8 active electrodes; therefore, the corresponding number of OA-based buffer amplifiers was chosen. In the block of restriction and protection, Schottky diodes provide protection against high-amplitude power surges of the defibrillator. Buffer amplifiers implemented on operational amplifiers included in the repeater circuit provide a large input impedance. Protection of the amplifier inputs from pulses of high-frequency interference from an electrosurgical instrument is implemented on the basis of the low-pass filter.

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The registration channel selection block includes an 8-channel multiplexer with differential switching of inputs. In this work, we selected a multiplexer as part of a 24-bit ADS1258 ADC. The amplification and filtering unit consists of a tool amplifier and a neutral electrode driver, which is based on a dual operational amplifier. Sigma-delta ADCs must have high resolution and also have a built-in amplifier with adjustable gain. The microcontroller MK is needed to control the blocks for selecting the registration channel, amplification and filtering, ADC, as well as for transferring data to a PC. To ensure the electrical safety of the patient, it is necessary to realize galvanic isolation both by the transmitted signal and by power. The device will be powered from the USB port. For galvanic isolation on power supply, it is advisable to use a DC / DC converter chip, which provides the required protection for the patient. To provide bipolar power to the circuit, an inverter of supply voltage of 5V is used.

To implement the next block, PIC18F4550 was chosen. This microcontroller allows you to transfer data in USB 2.0 format to a personal computer. Fairchild HCPL 2631 was used as an optical isolation element. Optical isolation is necessary to ensure the patient's electrical safety in case of current leakage on the USB port. The circuit power is supplied to the TME0505S DC-DC converter, which provides isolation of the circuit for power. At the output of the converter, a voltage of +5 V is formed. ADP3605 series DC voltage inverter is used to generate -5V negative voltage. To obtain the required voltage level + 2.5 V, the LM3670 voltage converter microcircuit is used, and the MAX660 inverter is used to generate a negative voltage of 2.5 V [2].

The developed device fully meets the applicable technical requirements.

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## **MAGNETIC LEVITATION OF CALCIUM PHOSPHATE PARTICLES AS NEW APPROACH FOR 3D SCAFFOLDS BIOFABRICATION**

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The main mineral component of bone is calcium phosphate (CP), so the application of 3D scaffold based on CP is highly promising for bone defects replacement [1]. Synthetic calcium phosphate granules can be used as building blocks for 3D printing of tissue-engineered bone scaffolds. One of the promising 3D printing technologies is formative technology that engages the simultaneous assembly in the whole volume of fabrication chamber. Magnetic levitation, as a special case of formative technology, can be considered as a novel way to fabricate biomaterials and scaffolds for tissue engineering, including the assembly of three-dimensional scaffolds from single CP diamagnetic granules [2-3].

The aim of this study was to demonstrate a principal feasibility the 3D fabrication of biocompatible CP-based constructs using magnetic levitation.

It was found that  $\alpha$ -tricalcium phosphate ( $\alpha$ -TCP) particles with average size 250-500  $\mu\text{m}$  and certain porosity can be assembled in 3D scaffolds via levitational formative method by using non-homogeneous magnetic field in the presence of 3M  $\text{Gd}^{3+}$  salts at room temperature. The resulting CP-based constructs demonstrate non-toxicity and high biocompatibility.

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Thus, in the present work we show that magnetic levitation of calcium phosphate particles is a promising approach for rapid 3D fabrication. Taking into account the good surface properties of the obtained CP-based constructs, these data opens a unique opportunity for biofabrication of tissue-engineered scaffolds based on CP and living cells.

The reported study was funded by RFBR according to the research project № 18-29-11076.

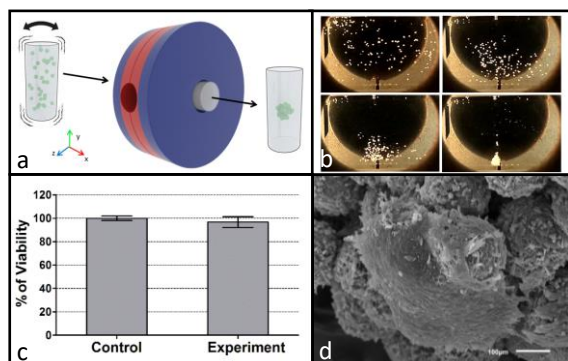


Figure 1. (a) Schematic showing of installation and scaffold fabrication. (b) The dynamics of assembly of  $\alpha$ -TCP particles. (c) The effect of medium after 4-days incubation with CP-based 3D scaffold on the SHED cell viability (Alamar Blue assay, 72 h). (d) SEM image of CP-based 3D scaffold with SHED spheroids on the surface after 7 days incubation.

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## **DEVELOPMENT OF METHODS AND MODELS OF ANALYSIS OF THE NETWORK STRUCTURE OF THE SKIN MELANOMA IMAGES**

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In the early stages of melanoma development, the symptoms are mild and do not look dangerous to the patient, so the person is in no hurry to see a doctor. The number of highly qualified specialists is small, and there are more and more patients. The lack of automated diagnostic systems further complicates the situation.

One of the first studies of methods for extracting pigment network lines was the system proposed by S. Fischer, which was based on the alignment of the image histogram and the application of certain morphological operations. M. Fleming used differential geometry and Hessian functions for the same purpose. Also the application of methods based on the Hessian. An option for using energy masks and a matrix of the dependence of the neighboring average level is packaged. M. Sadeghi in her research applied graph theory to highlight the grid structure. The pigment pattern is distinguished using a combination of spectral (Fourier transform) and structural (median filtering, morphological operations) methods. The work of M. Pap (M. Pap) presents the use of adaptive histogram alignment with the subsequent application of the Laplace operator to the Gaussian filter, and the algorithms proposed in the study are based on the Gabor filter.

Thus, it is seen that the analysis of the grid structure on dermatoscopic images of pigmented skin neoplasms is relevant, which is confirmed

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by a large number of studies in this area. Therefore, a proprietary approach to isolating the pigment network lines was proposed, which contributes to the study of the diagnosis of melanoma.

The system is designed to work with digital dermatoscopic images of melanocytic neoplasms of the skin, on which the neoplasm is directly [1,2].

Before the main image processing, a bilateral filter is applied to eliminate the noise present on it. Such a filter smooths the image, but at the same time leaves the subject clear. Then, matched filters are applied, oriented in four directions: vertical, horizontal and two diagonal. The task of applying these filters is to highlight extended objects in the image, which are the desired lines of the pigment network. The result of the study was a system for isolating the pigment network line on melanocytic skin neoplasms and calculating the characteristics of the selected area. The resulting program allows you to view the image, process it, observe the processing result and save it, as well as build histograms based on the calculated characteristics. In the future, when finalizing the functionality of the resulting program and improving its efficiency and speed, it can be used as an integral element of the melanoma recognition system, because pigment network characteristics in melanocytic skin neoplasms play an important role in the diagnosis of melanoma.

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## **STUDY OF PRODUCTS OF PHOTONUCLEAR SELENIUM REACTIONS**

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Positron-emitting radionuclides are used to diagnose cancer. One of the promising medical radionuclides is  $^{72}\text{As}$  ( $T_{1/2} = 26$  h, positron energy = 2.5 MeV), which can be obtained in a generator from  $^{72}\text{Se}$ .

the photonuclear production of the isotope of arsenic  $^{72}\text{As}$  was studied in this work. The isotope of arsenic was produced from selenium of a natural isotopic composition. The formation of  $^{72}\text{As}$  occurs in two ways - through the direct reaction of  $^{74}\text{Se}$  ( $\gamma, np$ )  $^{72}\text{As}$ , and also as a result of the decomposition of  $^{72}\text{Se}$  formed by the reaction of  $^{74}\text{Se}$  ( $\gamma, 2n$ )  $^{72}\text{Se}$ . The selenium powder was irradiated by bremsstrahlung photons obtained as a result of braking of 55 MeV electrons on a tungsten plate. Experiment was carried on a split microtron at the Research Institute of Nuclear Physics, Moscow State University. The gamma spectra of the reaction products were recorded on a HPGe-spectrometer [1]. It is shown that the method can be used to produce  $^{72}\text{As}$ .

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## **HALLOYSITE NANOTUBES WITH IMMOBILIZED GOLD NANOPARTICLES AS SENSITIZER FOR SPATIALLY AND TEMPORALLY LOCALIZED PHOTOHYPERTHERMIA**

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Halloysite clay is a two-layered aluminosilicate, chemically similar to kaolin, which has hollow tubular structure in the submicrometer range. Kaolin sheets are rolled into tubes because of the strain caused by lattice mismatch between adjacent silicone dioxide and aluminum oxide layers [1]. As for most natural materials, the size of halloysite particles varies from 50 to 70 nm in external diameter, ca. 15 nm diameter lumen and  $1 \pm 0.5 \mu\text{m}$  length [2]. Halloysite exhibits interesting physical and chemical properties due to predominantly hollow tubular structure and site dependent chemistry. A significant advantage of halloysite is its availability and relevantly low price compare to tubular nanomaterials like carbon nanotubes [3].

Currently, a number of attempts have been made to develop novel, efficient and environment-friendly antibacterial materials. A wide variety of antibacterial materials have been reported to prevent attachment and proliferation of microbes [4]. However people have often come across the fact that antibiotics do not help during the treatment of many infectious diseases. Their use is limited due to problems of bacterial resistance to antibiotics. Nanostructures containing silver, copper, zinc,

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iron oxides, and their combinations are well known for killing even antibiotic resistant bacteria, which is why they are widely applied for making materials with antibacterial properties. The use of templates helps to overcome the aggregation of particles and their release to the environment. Halloysite has great potential as a carrier for metal particles grafting and metal complexes formation [5].

Halloysite nanotubes (HNTs) with surface-immobilized gold (Au) nanoparticles (NPs) with mean size of about 6 nm were explored as sensitizers for spatially and temporally localized photohyperthermia (PHT). The structure and plasmonic properties of NHTs: Au nanotubes were analyzed by means of the transmission electron microscopy and optical extinction spectroscopy, respectively. A remarkable PHT response under cw and pulsed laser photoexcitation in the plasmonic extinction band near 0.5  $\mu\text{m}$  was measured for HNTs: Au dispersed in water, while the same photoexcitation of pure HNTs without Au NPs did not result in any remarkable heating. In-vitro experiments with infusoria cells have revealed an effect of the PHT induced suppression of the cell viability under cw and especially pulsed photoexcitation. The obtained results indicate that NHTs/ Au nanocomposites are promising nanosensitizers for biomedical applications as antibacterial treatment and mild cancer therapy.

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**POLYELECTROLYTE MULTILAYER CAPSULES FOR THE  
DELIVERY OF ANTICANCER DRUGS: PREPARATION AND  
EVALUATION IN 3D IN VITRO MODEL**

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Among a large number of different drug delivery systems, polyelectrolyte multilayer capsules (PMC) are of great interest.

The aim of the study was to obtain a unique anticancer drug delivery system, namely PMC based on dextran sulfate and poly-L-arginine (DS/Parg) loaded with doxorubicin (DOX) and to study their cytotoxicity and accumulation efficiency in an *in vitro* model. The capsules were fabricated by layer-by-layer (LbL) technique using vaterite particles (500 nm) as sacrificial templates. An approach was developed for the simultaneous miniaturization of capsules to a size of 260 nm and loading of DOX [1].

In this work, the physicochemical properties of PMC were also studied (average size, encapsulation efficiency,  $\zeta$ -potential, etc.). The cytotoxicity of these capsules was studied on human breast adenocarcinoma (MCF-7 cells) using the MTT test. The efficiency of accumulation and localization of the system (DS/Parg)-DOX in a 3D model (tumor spheroids formed by adding a synthetic cyclic RGD-peptide to a monolayer of cell culture [2]) was investigated using confocal microscopy. It was found that these capsules after 15 minutes of incubation with tumor

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spheroids were adsorbed on their external surface, and then evenly  
spread within its internal volume for 1 hour.

Thus, DS/Parg-based PMC can be used as a promising antitumor  
therapy system.

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**CREATION OF ACTIVE PHOTOCATALYTIC  
NANOSTRUCTURES OF TITANIUM DIOXIDE BY USING  
THERMAL ANNEALING OF PRECURSOR LAYERS**

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Creation effective generating active forms of oxygen structures by light-activated wide-range. Such structures may be applied in case of antibacterial systems.

It could be interesting to compare the effectiveness of the structures established on colloidal nanoparticles of titanium dioxide and the structures on nanoparticles formed as a result of thermal annealing precursor layers.

Firstly, we use Langmuir-Blodgett technique for the preparation of organic ultra-thin is a traditional object of research. This technique has one disadvantage: the thin films were washed off the substrate.

Our samples were received by picking up the titanium dioxide thin films from the surface of distilled water. Then some samples were annealing in stove in 500°C. We have create active photocatalytic nanostructures of titanium dioxide by using thermal annealing of precursor layers. This nanostructures generate the active forms of oxygen. This active forms of oxygen could be used in antibacterial therapy.

After that we compare graphs of absorption sample with annealing and without it in photospectrometer. We got two different types of additions. For the samples without annealing we have graphs with strongly marked peak about 430 nm. Another samples which were annealing at 500°C have peaks which decrease by increasing irradiation time.

This research give us expected results. We registrate that the peak which was connected to absorption intensity decreased with increasing of exposure time. This fact connected with ability of titanium dioxide nanostructures to create the active forms of oxygen.

At the end of our research we've got the nanostructures which could create the active forms of oxygen. In future, we will improve this feature and apply it to bacterial therapy.

## VISIBLE LIGHT ACTIVATED TITANIA NPs BASED STRUCTURES

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Titania nanoparticles (NPs) are in a focus of many studies because of their high photocatalytic activity [1]. This feature of Titania NPs is due to their ability to generate reactive oxygen species (ROS). The presence of a large concentration of ROS in bacterial cells leads to their destruction, and thus the antibacterial activity of titanium dioxide is carried out. However, utilization of Titania NPs as antibacterial systems is limited because of its high band gap energy (3.2 eV). It means that Titania NPs can be activated only by UV radiation, which is harmful for living systems. Up to now some approaches to increase Titania NPs activity under visible light have been demonstrated. It has been shown that a combination of Titania NPs with semiconductor quantum dots (QDs) is the most promising because of unique optical and electrical QD properties [2]. Hybrid structures with QDs can act effectively under the visible irradiation, owing to photoinduced electron transfer from QDs to Titania NPs. The suitable relative position of the donor's (QDs) and acceptor's (Titania NPs) conduction bands with minimal donor-acceptor distance are required for achieving the efficient electron transfer in the structures [2, 3]. Thus, finding the way to develop QDs/Titania NPs structures with excellent electron transfer efficiency will allow to apply these structures in antibacterial therapy.

In this work, the multilayered QDs/Titania NPs hybrid structures have been formed by Langmuir-Blodgett technique that provides a minimal distance between nanoparticles [4]. We have used 2.6 nm core CdSe QDs because their conduction band position is the best for photoinduced electron transfer to Titania NPs [5]. We have found that lumi-

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nescent fractions of the QDs are capable of very fast electron transfer to Titania NPs' conduction band ( $k_{ET} = 4 \cdot 10^{10} \text{ s}^{-1}$ ). It allows to realize  $85 \pm 5\%$  electron transfer efficiency in the structures. At the same time the analysis of ROS generation of the structures under visible light has shown that average electron transfer efficiency is  $55 \pm 5\%$  because of the dark fraction in the QD ensemble. Therefore, reducing the QD dark fraction improves electron transfer efficiency in QDs/Titania NPs structures and it will lead to advent of a new extremely efficient antibacterial agent.

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## THE FEMALE PHANTOM EFFECTIVE DOSE AT CROSSING THE EARTH RADIATION BELT

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In Apollo missions, astronauts are exposed to corpuscular, x-ray and gamma radiation with a wide range of energy. According to available publications, the radiation dose of an astronaut with the quiet Sun is formed mainly when crossing the Earth radiation belts. The average absorbed dose was 0.41 rad [1].

In one of the article [2], the van Allen belts overcoming scenario is described in detail and the equivalent dose value is given [2]. In this regard, the following task was posed: Calculate the radiation dose for the anthropomorphic model of the astronaut and compare the result with the official values of "NASA" and the values of conspiracy theorists.

The MCNPX code from the MCNP family was chosen as the transport code [3], which allows to take into account all reactions whose products form the astronaut's radiation dose using the universal «TALYS» nuclear data library [3].

Of all the types of radiation that exist in the van Allen belts, protons are the main source of danger – about 90 % of the radiation dose, the remaining 10 % of the radiation is the x-rays of the solar wind. The range of proton varies from 20 to 1000 MeV.

A sphere of aluminum with a thickness of  $7.5 \text{ g/cm}^2 \rightarrow 2.8 \text{ cm}$  was adopted as a command module – the equivalent thickness of the command module shielding [1]. The internal inner radius of the model is 160 cm, which provides a volume equal to the volume of the real compartment.

The astronaut was modeled by an anthropomorphic female phantom from the series - MIRD Humans [4].

In the calculation the values of absorbed ("physical") and equivalent dose in organs and tissues of the phantom were obtained, as well as the

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effective dose during the passage of the Earth radiation belt according to the scenario taken from the Internet [2]. Table 1 shows the absorbed and equivalent dose values for some organs.

Table 1 – Absorbed and equivalent dose to the organs of the anthropomorphic phantom when crossing of the Earth radiation belt according to the scenario [2]

Cell	Name	Absorbed dose (Gy)	Equivalent dose (Sv)
4	Legs	7.79E-1	4.32E+0
7	Skin	7.87E-1	3.67E+0
13	Urinary bladder	2.12E+0	1.11E+1
15	Ovaries	2.94E-1	1.88E+0
19	Large bowel	1.07E+0	5.94E+0
21	Leg bones	5.72E-1	2.82E+0
24	Hand bones	2.84E-1	1.76E+0
64	Uterus	4.96E-1	3.10E+0
65	Thorax	1.44E-1	8.44E-1

Further, the effective dose was calculated – 2.3 Sv taking into account the weighing coefficients for the organ or tissue [5].

The doses obtained in our computational experiment are many times higher than the official data on the dosimetry of the Apollo missions [1]. The Flights under this scenario are impossible. The radiation dose is too high and the probability of survival after such exposure is extremely small.

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## PROLONGATION OF NANOPARTICLES BLOOD CIRCULATION VIA MACROPHAGE INHIBITION

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The use of nanomaterials for targeted drug delivery is a promising direction of modern biomedicine [1]. However, many types of nanoparticles that have been shown to be effective *in vitro* are unsuitable for *in vivo* use. One of the main reasons for this is the rapid removal of particles from the bloodstream into the liver and spleen and their uptake by macrophages [2]. In order to prolong the circulation of nanoparticles in the bloodstream, we inhibited the ability of macrophages to phagocytosis using blocker particles.

Various nano- and micro- particles were used as blocking particles. The effectiveness of the method varied greatly depending on the basic physicochemical characteristics of the particles.

Non-invasive real-time quantitative analysis of nanoparticles in the bloodstream was carried out based on the nonlinear magnetization of superparamagnetic nanomaterials in response to an applied alternating magnetic field (MPQ-detection) [3]. The method eliminates the influence of dia- and paramagnetic materials and has a sensitivity of several picograms of magnetic nanoparticles [4].

Inhibition of the ability of macrophages to phagocytosis with nanomaterials made it possible to significantly prolong the circulation of particles in the bloodstream and also affect their biodistribution. In addition,

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tion, we studied how the characteristics of blocking particles affect the effectiveness of the method.

Thus, the inhibition of phagocytosis of particles can be a solution to the problem of rapid elimination and uptake of nanoagents by macrophages of the liver and spleen and will allow to expand the range of particles used *in vivo*.

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## IMPACT OF X-RAY TUBE VOLTAGE ON RADIOSENSITIZATION EFFECT OF GOLD NANOPARTICLES

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Nanoparticles (NPs) of metals with a high atomic number (Z), particularly gold nanoparticles (GNPs), are a new promising class of anti-tumor radiosensitizers both for classical photonic and particle radiotherapy (RT). The selection of optimal irradiation conditions that provide the highest efficacy of NPs radiosensitization is a key factor for their use. We investigated the dependence of efficacy of radiation induced damage of the plasmid DNA in the presence of  $26 \pm 2$  nm GNPs on X-ray tube voltage. The GNP concentration was 2.4 mg/mL (1.5 NPs per one DNA molecule). Irradiation was carried out on a RUST-M1 X-ray machine. The voltage on the X-ray tube was varied from 100 to 200 kVp; the dose rate was 0.2 Gy/min. To quantify magnitude of radiosensitization, we used the sensitizer enhancement ratio (SER):

$$\text{SER} = \frac{D_{\text{control}}}{D_{\text{GNPs}}}, \quad (1)$$

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where  $D_{\text{control}}$  is dose for the observed effect in the control sample (without GNPs),  $D_{\text{GNPs}}$  is the dose evoking the same effect in the presence of GNPs.

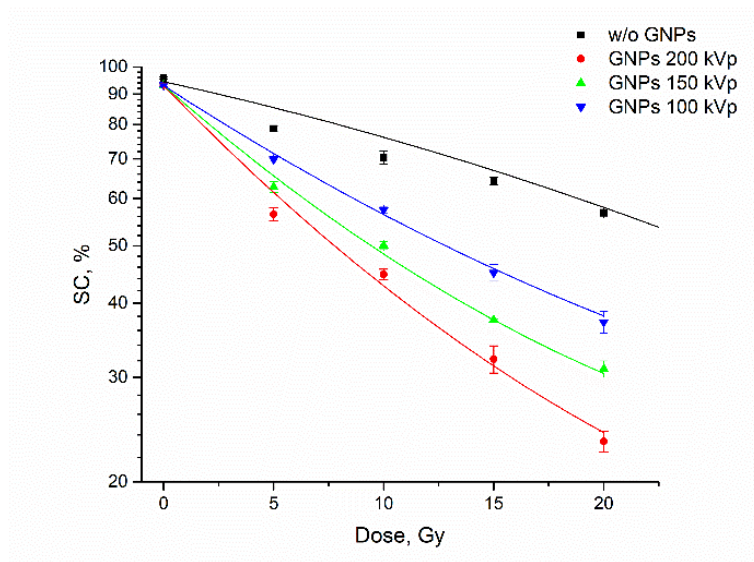


Fig.1. The dependence of plasmid DNA damage on radiation dose at different voltage on the X-ray tube. No GNPs (200 kVp; black). 2.4 mg/mL GNPs: 100 kVp (blue), 150 kVp (green), 200 kVp (red).

The increase in voltage on the X-ray tube significantly increased the radiosensitizing effect of GNPs. The highest SER equal to  $5.84 \pm 0.84$  was observed at 200 kVp. Reduction of voltage on the X-ray tube to 150 kVp and 100 kVp led to a smaller magnitude of radiosensitization ( $4.96 \pm 0.90$  and  $3.98 \pm 0.76$ , respectively). Thus, voltage on X-ray tube is one of the key parameters, that must be optimized to accomplish GNPs radiosensitization efficacy in practical settings.

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**DEVELOPMENT OF THE DISTRIBUTED STRUCTURE OF  
FORMATION OF KNOWLEDGE BASES IN THE DIAGNOSIS  
OF MINIMUM RESIDUAL DISEASE**

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Currently, the diagnosis of malignant neoplasms of the lymphatic and hematopoietic systems (hemoblastoses) is one of the urgent medical and social problems of modern oncology.

To search for objective criteria, work is underway to compare immunophenotype and computer microscopy data in the diagnosis of leukemia. A correctly formulated diagnosis allows the doctor to determine the clinical course, standard therapeutic measures, and the prognosis of the disease.

Among the problems, relapses in children with acute lymphoblastic leukemia (ALL) are also worth noting. The results of treatment of children with relapses are determined by several factors: the period of its development, the localization of relapse and the immunophenotype of tumor cells.

In modern treatment protocols for ALL in children, in addition to standard prognosis factors, it is possible to separate patients taking into account the assessment of the number of residual blasts in the bone marrow - the minimum residual disease (MOB).

The standard risk group is the presence of up to 0.1% of MOB cells among myelokaryocytes. The intermediate risk group includes patients with a residual blast level from 0.1 to 10.0% in CM. The high-risk group includes patients with the number of MOB cells of 10.0% or more.

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Recently, numerous attempts have been made to automate microscopic studies to increase the accuracy of detection of young forms of cells.

Automated microscopy is a research method based on digital processing and recognition of objects on microscopic images. The use of which makes it possible to objectify the obtained data in the form of numerical indices when studying the structure of nuclear chromatin filaments, while qualitative microscopes are obtained by visual microscopy.

So, in the context of the diagnosis of MOB, it is computer microscopy that can improve the accuracy of the differentiation of blasts and lymphocytes in the bone marrow of patients during treatment. This will provide an opportunity to improve control over the disease. It is important that it is on the basis of regular analyzes of MPS in the patient's bone marrow that it is possible to suspect an early onset of relapse and to start a comprehensive examination at the same time.

In the work, several approaches are proposed to solve the problems described. The first is the development of a classifier system with the ability to separate blood cells and bone marrow in cell groups. The second is the creation of distributed software to optimize the stages of forming the knowledge bases necessary when replenishing cells in various groups and bringing them to equivalent values.

The reported study was funded by RFBR according to the research project № 18-29-09115

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## **FABRICATION OF SAMARIUM NANOPARTICLES BY FEMTOSECOND LASER ABLATION IN LIQUIDS**

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Nuclear nanomedicine provides unique opportunities to treat tumors due to its targeting ability, good loading capacity and enhanced retention. This field of science has become increasingly important over the last decades, promising an attractive and powerful alternative to conventional chemotherapy. However, synthesis of radioactive agents in nanoscale is rather challenging. Here, we have chosen a different way. First, we produce nanomaterials and only after that “activate” them into radioactive form. Our approach is based on synthesis of enriched  $^{152}\text{Sm}$  oxide nanoparticles (NPs) by two-step femtosecond laser ablation and fragmentation in liquids. We show that the direct ablation of a samarium oxide target leads to widely size- and shape dispersed populations of NPs. We also demonstrate that application of additional laser fragmentation step allows one to produce spherical NPs and finely tune their size between 7 and 70 nm. The formed NPs are of importance for catalytic and biomedical applications.

The authors acknowledge financial support from Russian Science Foundation (Grant № 19-72-30012).

## DESIGN OF NOVEL STIMULI-SENSITIVE LIPOSOME-BASED DRUG DELIVERY CARRIERS

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Design of a controllable and targetable drug delivery system is imperative and important to reduce the side effects and enhance the therapeutic efficacy of drugs. There is a number of approaches to solving this problem; one of the most popular approaches are biomimetic lipid vesicles - liposomes as encapsulation agents and drug carriers. This method has significant advantages due to the non-toxicity and complete biocompatibility of the lipids used, since lipids are the main structural components of biological cell membranes. A wide range of possible liposome synthesis techniques is also an advantage, since it allows you to vary the size of the resulting liposomes, for example, allowing drug capsules to penetrate through the smallest capillaries (5-10  $\mu\text{m}$ ), or, on the contrary, to achieve the accumulation of carrier capsules directly in tumors, due to the enhanced permeability and retention effect (EPR).

Various functional inclusions allow liposomes to provide new advantages as carriers of drugs. For instance, gold or magnetite ( $\text{Fe}_3\text{O}_4$ ) nanoparticles can be incorporated directly into the liposomal membrane. Magnetite particles have magnetic and semiconducting properties, and therefore can provide sensitivity to external electric and magnetic fields. Gold particles can act as nano-sized antennas for an external electric fields and electromagnetic influences. Exposure to ultrashort electric

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field pulses of 10 ns duration and intensity of the order of  $1 \times 10^7$  V/m leads to effective liposome decapsulation —destruction of the liposome membrane and release of encapsulated substances into the outer space. The mechanism of this effect is similar to the processes leading to irreversible electroporation of the membranes, however, the feature of this case is a significant amplification of the local electric field by conducting inorganic nanoparticles, which are sensitive to external controlling physical stimuli and provide high selectivity of such effects.

Another approach to achieving controlled release of drugs from magnetic liposomes is to use an external magnetic field. An external magnetic field not only allows the localization of magnetic carrier capsules in a specific area of the body, but also leads to the release of liposomes containing magnetite nanoparticles in the structure of the liposome membrane. The advantage of an external magnetic field is its complete harmlessness to humans. In particular, it was experimentally shown that placing a solution of nanocomposite liposomes between the poles of a magnet creating a field of 1.9 kOe intensity leads to the release of liposome contents. In this case, unlike the use of a pulsed electric field, liposome destruction does not occur - under the influence of an external magnetic field, liposomes reversibly change their shape from spherical to ellipsoidal, which leads to deformation of the liposome membrane and a change in its permeability. A theoretical analysis of this effect indicates that such deformations are caused by the desire of the system to minimize the magnetostatic energy of magnetic liposomes, while the minimum free energy of the magnetic liposome is achieved for the shape of an ellipsoid with an elongated half-axis oriented along the field, which corresponds to the obtained experimental results.

This work was financially supported by the Russian Foundation for Basic Research (project code 18-29-02080).

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**IMPLEMENTATION OF MICRODOSIMETRIC MODELS FOR  
CALCULATING THE RELATIVE BIOLOGICAL EFFICIENCY  
OF PROTON AND CARBON ION BEAMS IN THE RTS&T  
CODE SYSTEM**

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The exact calculation of the delivered dose in the process of irradiating tumors with proton and carbon ion beams is one of the most important components of the process of planning radiation therapy. Today there are two advanced microdosimetric models for calculation the relative biological efficacy of radiation, that are used in clinical practice. This is Microdosimetric Kinetic Model (MKM) and Local Effect Model (LEM). This work contains descriptions of the features of the implementation of the MKM and LEM as models that are included in the RTS&T software package [1-2]. The results of theoretical and experimental studies of the main microdosimetric characteristics for cellular structures placed in homogeneous water phantoms irradiated with 454 MeV/u  $^{12}\text{C}^{6+}$  ions are presented [3].

This report compares the calculated (RTS&T using different hadron generators and several methods for calculation of ionization losses and the standard version of the FLUKA code) with experimental data for the depth-dose distribution, flux- and dose-averaged linear energy transfer from the primary carbon ion beam. There is also a comparison of the depth-RBE distributions at different levels of survival and biological dose distributions, calculated for 9 types of cellular structures using the

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RTS&T and FLUKA codes. In conclusion, the results of modeling the parameters of modified Bragg curve obtained in the framework of RTS&T for the conditions of irradiation a homogeneous water phantom with a carbon ion beam using a ridge filter are given in comparison with the experimental results.

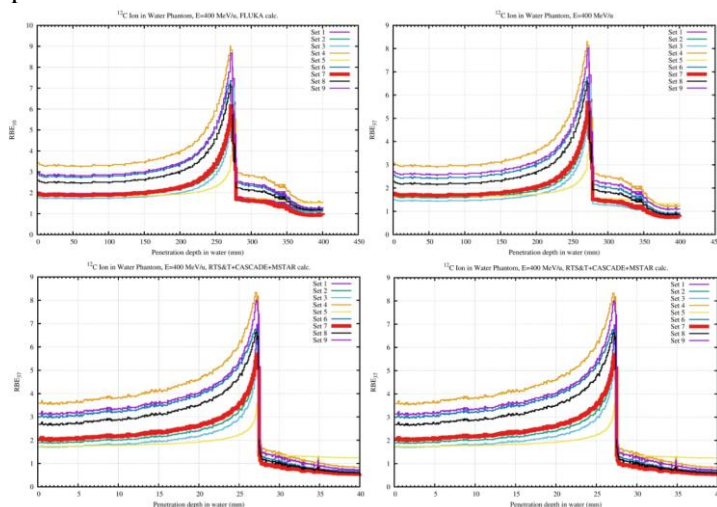


Fig.1. Depth RBE distributions obtained in the framework of the MKM model based on  $LET_D$  values calculated using the FLUKA (first two graphs) and RTS&T (second two graphs) codes. Graphs are given for 10% (the left ones) and 37% (the right ones) cell survival in the water phantom.

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## LOW INTENSITY BEAM EXTRACTION MODE ON PROTOM SYNCHROTRON FOR PROTON TOMOGRAPHY IMPLEMENTATION

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ProtonVDA has developed a highly efficient and inexpensive proton tomography system based on solid state photomultipliers and fiber detectors [1-2]. One of the main advantages of this system is a lower, compared with similar X-ray imaging systems, equivalent dose that is received by the patient. This feature is explained by the accurate reconstruction of the tracks of individual protons passing through the patient's body, as well as by using a special mode of operation of the accelerator with extremely low intensity of the extracted proton beam during the entire tomography time.

The purpose of this work is to show the possibility of using the developed proton tomography system as part of the Russian proton therapy complex (PTC) «Prometheus», which has been working in clinical mode for more than 3 years [3-5], as well as other proton therapy facilities that based on Protom synchrotron. This synchrotron is capable to accelerate protons to energy up to 330 MeV. This fact makes proton tomography of entire patient body possible. The use of a synchrotron will significantly simplify the design of the scanner, and makes it cheaper.

A special tomographic accelerator operation mode was developed and tested. It will increase the percentage of useful proton events regis-

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tration that are used for further proton track reconstruction. This mode will increase the efficiency of the tomography setup and reducing the dose. The report presents the results of the first testing of the tomographic beam extraction mode at the Protom synchrotron; examples of reconstructed proton scanner tomograms for physical objects and tissue-equivalent phantoms in case of irradiation with a proton cyclotron beam.

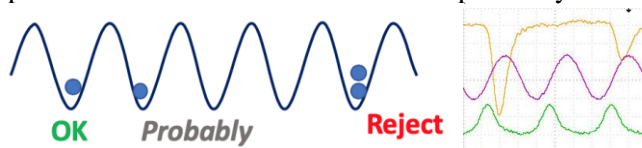


Fig.1. The principle of detection individual protons (left one) and example of double and single proton extraction per beam turn inside the synchrotron (right one)

This work shows the possibility of the PTC «Prometheus» (as well as other facilities based on the Protom synchrotron) to operate in a special proton beam extraction mode, in which single protons are released for each revolution, that allows such facilities to work effectively in tomographic mode.

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**NANOPORE SEQUENCING, THIRD GENERATION  
TECHNOLOGY, REDUCES TIME AND COST OF  
SEQUENCING**

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Over the past fifteen years second generation sequencing or SGS platforms applied jointly with innovative computational approaches have revolutionized the field of biomedical research leading the way for a new cycle for personal genomics and decreasing the time for sequencing of full human genomes at affordable prices. Albeit SGS technology has ultimately changed our ability to analyze the genetic variation of any organism, it is apparent that the short reads of 100 to 500 base pairs generated by these platforms are insufficient to resolve complex genomic structures that are relevant for examining and comprehending evolution, diseases, viruses and mutations.

The past few years have seen the development of a third generation of sequencing or TGS technologies based on single-molecule real-time and nanopore sequencing, which examine single molecule of DNA and are capable to produce sequences much longer than those of SGS methods.

Nanopore sequencing involves the transit of a single stranded DNA molecule through a nanoscopic pore and the contemporary measurement of its effect on an electric current, when disruption of ionic current is measured in signal trace. Raw current signals are then utilized to interpret the sequence of the single stranded DNA by means of machine learning algorithms[1].

Oxford nanopore technology, ONT, enables identification of a broad range of analytes, such as of DNAs, RNAs, microRNAs and proteins. The nanopore is inserted into an electrically resistant membrane created

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from synthetic polymers, a potential is applied across the membrane resulting in the current flowing only through the aperture of this nanopore. Single molecule that enters the nanopore causes characteristic disruption in the current, by measuring this disruption the molecule can be identified.

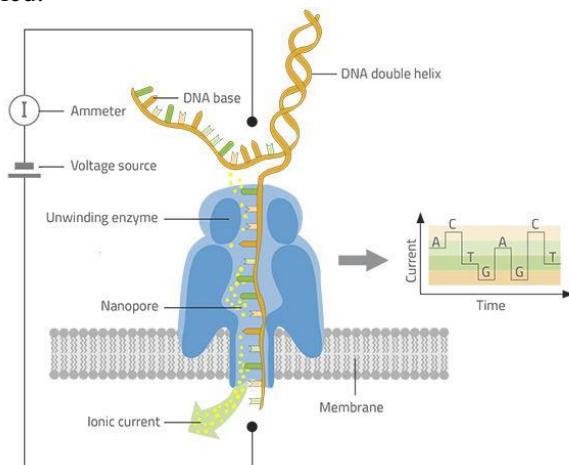


Fig.1. Nanopore sequencing scheme [2]

ONT MinION is the only portable, real-time device for DNA/RNA nanopore sequencing being commercially available, simply by paying a starter-pack fee of \$1,000 with single molecule data accuracy of 95% [3], thus having simplified the sequencing procedure and making it affordable and accessible in remote locations for clinical research, microbiology, human genetics, cancer research, biodefense and forensics.

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## **DSB CLUSTERS DISTRIBUTION FOLLOWING IRRADIATION OF 3D CHROMATIN STRUCTURES WITH FAST NITROGEN IONS**

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DNA double strand breaks (DSBs) constitute the most significant molecular lesions induced after irradiation of cells with charged particles. The distribution of DNA fragments length measured by pulse field gel electrophoresis carries information about the clustering of DSBs, i.e. heterogeneous distribution of breaks along the DNA molecule. For cell irradiation by charged particles the distribution of DNA fragment lengths differs significantly from the homogeneous distribution specific for random breakage mechanism or low-LET radiation. The quantitative interpretation of the heterogeneous DNA fragmentation after cell irradiation by ions requires detailed knowledge of stochastic structure of charged particle tracks as well as information about 3D structure of biological targets within the cells, i.e. 3D chromatin structure.

Using polymer physics methods we modeled spatial conformations of 1 Mbp chromatin domains with different spatial organization, as to polymer globule, rosette-like and decondensed, looped conformations. Chromatin globule was obtained during the condensation of chromatin fiber to the dense state using molecular dynamics approach. Stochastic track structures of fast ions with LET = 50 and 125 keV/ $\mu\text{m}$  were simulated by DeTrack and Geant4 packages. We calculated the distribution of DNA fragment lengths for different irradiated chromatin structures. It was demonstrated that frequency of small DNA fragments (~5 kbp) was impacted mainly by molecular structure of chromatin fiber. Frequencies of intermediate and large DNA fragments (more than 100 kbp) were determined by folding of chromatin in loops within the Mb-sized domains. Thus, spatial organization of chromatin efficiently contributes to the DNA DSBs clusters induction by fast ions.

## **CYTOTOXICITY ANALYSIS OF SILICON NANOPARTICLES MODIFIED BY BIOCOMPATIBLE POLYMER**

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Nanoparticles nc-Si are light-emitting particles on the nanometer scale that have emerged as a new class of fluorescent labels for chemical analysis, molecular imaging, and biomedical diagnostics. A distinctive feature of nc-Si is a high absorption coefficient in the near UV and blueviolet range and the ability to transmit light in the visible region of the spectrum [1].

The aim of this work is to analyze the toxicity of polymer-modified composite materials based on nanocrystalline silicon (nc-Si) as an alternative to organic fluorescent dyes and quantum dots. For hydrophilization of silicon nanoparticles, their surface was modified by the amphiphilic biocompatible polymer cremophore. Silicon nanoparticles (nc-Si) with an average diameter of 4.5 nm were synthesized by heating of SiO at 1150 °C. The sedimentation and aggregation stability of the particles in water was analyzed. Colorimetric MTT-assay of the cytotoxicity of the nanoparticles modified with polymers towards human cervical carcinoma cell line HeLa showed no toxicity against the cells in culture at particle concentrations of up to 50 µg/ml. Subcellular localization of silicon nanoparticles in HeLa cells was shown by confocal fluorescence microscopy.

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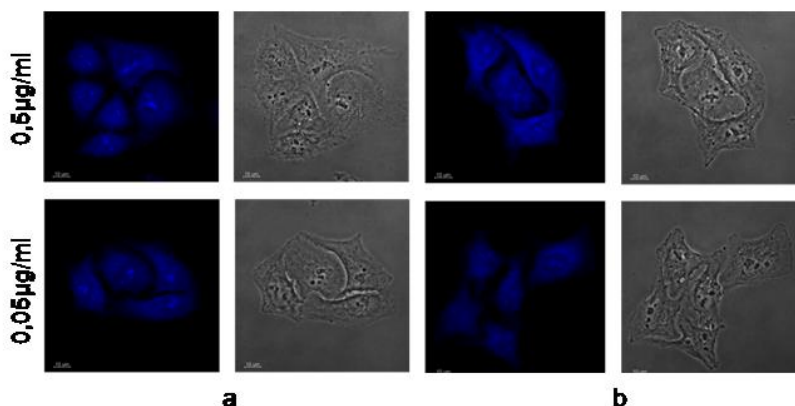


Fig.1. Photoluminescence of the unmodified silicon nanoparticles nc-Si (a) and nanoparticles modified by Cremophor RH 40 ( $D=36$  nm) (b) in HeLa cells. To the right of the photoluminescence image are photographs of the same cells obtained by visible light microscopy. The concentrations of the nanoparticles in the growth media are indicated on the left.

The photoluminescence of silicon nanoparticles was detected using an excitation at 405 nm and emission was registered at 706 nm. It should be noted that the particle concentration by an order of magnitude leads only to a slight decrease of the intensity of the photoluminescence that can be explained by the accumulation of the particles in the cells. Second, the photoluminescence of the Cremophor modified nanoparticles is observed in the cells as well. Thus, the ability of nanoparticles to penetrate cells and emit light is preserved after hydrophilization of nc-Si by Cremophor. Therefore, the obtained polymer-modified nc-Si particles can be recommended for the purposes of bioimaging *in vitro* and *in vivo*.

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## **RADIOSENSITIZING EFFICACY OF GOLD POLYACRYLATE IN RADIOTHERAPY STUDY**

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Oncological diseases are currently one of the leading causes of human death. Main methods of malignant tumors medical treatment are: surgical removal, chemotherapy and radiotherapy. According to WHO data, up to 70% of oncology patients need radiation therapy. Consequently, today the issue of increasing the effectiveness of radiation therapy is relevant. One of the ways to increase the efficacy of the ionizing radiation use in treating tumors is to increase the radiosensitivity of tumor tissue by the use of radiosensitizers. [1-2]

In this work, radiosensitizing properties of the drug based on gold polyacrylate were studied. Promising results on potential antitumor efficacy of this drug were obtained earlier elsewhere. [3-4] Current study was performed on female C57Bl/6 mice weighing 20-22 g (nursery Pushchino, Moscow region). Melanoma B16F10 was used, as a tumor model. Tumor cells suspension was injected subcutaneously in the middle third of the right hind limb into the lower leg region. Gold polyacrylate was administered intraperitoneally at a dose of 11 mg / kg of gold in a volume of 0.2 ml. Irradiation was made with x-ray generator operating at 225 kVp and 13.3 mA and with an aluminum filter of 1 mm thick. The distance from x-ray source to the irradiated tumor was 26 cm. Animals were divided into four groups. The first group was the control group. The second group was administered with studied drug only. The third group was irradiated in a dose of 20 Gy only. The fourth group

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was administered with gold polyacrylate and irradiated in a dose of 20 Gy.

Tumor suppression was evaluated by tumor growth delay and increase in life span after the treatment. The average tumor volume for all four groups of mice are shown in Figure 1.

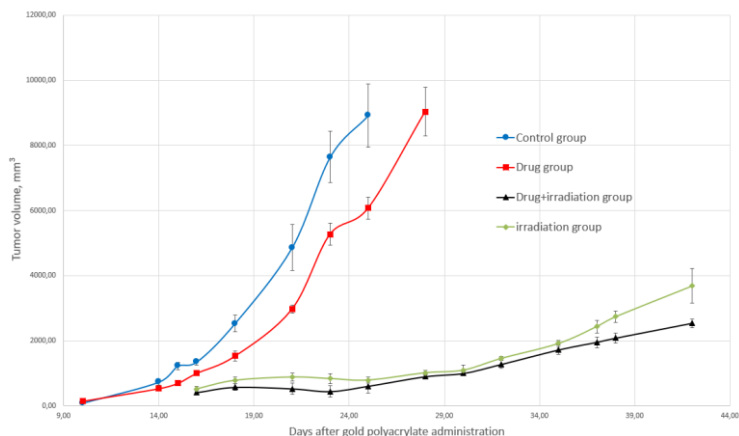


Fig.1. The average tumor volume at different groups of mice after irradiation.

The study of the antitumor efficacy of gold polyacrylate as a radiosensitizer did not reveal statistically significant inhibition of tumor growth compared to control irradiation. However, the administration of gold polyacrylate prior irradiation increases the median of life span from 35 days post tumor inoculation for irradiated control group to 46 days for the group irradiated with gold polyacrylate administration.

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## **DOTS RECOGNITION ON IMAGES OF SKIN NEOPLASMS**

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Melanoma of the skin is one of the most dangerous human malignant tumors, often metastasizing to almost all organs. Primary diagnosis of melanoma is based on routine examination and dermatoscopy. The interpretation of the observed picture is ambiguous and expert assessment is required for the correct diagnosis. The result of the analysis is subjective and largely depends on the experience of the doctor. In this regard, it is important to create automated image analysis systems for the diagnosis of melanoma, which would act as a means of supporting decision systems.

One of the promising approaches to the diagnosis of melanoma is the use of the algorithm "Chaos and signs" [1]. “Dots” are the important structural elements for the analysis of tumors. The paper deals with the problems of automated “dots” allocation. A model of “dots” recognition on dermatoscopic images of skin tumors is proposed. The software is developed according to the presented model. The results of experiments on automatic recognition of “dots” on images of skin tumors are presented.

The developed software can be used as an part of the decision support system in the analysis of skin tumors. It will help to reduce the number of diagnostic errors in the diagnosis of melanoma.

The work was supported by the RSF project № 19-11-00176.

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## **IRREVERSIBLE AND REVERSIBLE LUMINESCENCE CHANGES IN CARBON DOTS STUDIED BY CONFOCAL MICROSCOPY**

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Carbon dots are a promising class of carbon-based fluorescent nanoparticles, the surface of which may contain functional groups. Carbon dots have a number of advantages, such as the availability and simplicity of synthesis, luminescence that can be rearranged along the wavelength, high photostability and biocompatibility with bioimaging potential.

Carbon dots were synthesized by the solvothermal method by dissolved citric acid and ethylenediamine in water. The obtained solution was heated for 5 hours at 200°C and then cooled down to room temperature. The sample for the study is a film obtained by evaporation from an high-concentration aqueous solution of carbon dots. When a 405 nm laser light was applied to a 50x50 µm section of the sample, an increase in luminescence intensity and light transmission was observed.

Figure 1 (right) shows the luminescence spectra of the film areas from carbon dots before (1) and after (2) laser exposure. Along with a 2-fold increase in intensity, a shortwave shift of 50 nm in maximum luminescence is observed.

The change in intensity and the shift in the maximum luminescence spectrum during laser exposure are irreversible; they are supposedly caused by photo-influence on the internal structure of carbon dots. These processes do not depend on the ambient temperature and are not caused by the local heating of the area illuminated by the excitation laser. To confirm this, the optical properties of the obtained film in the temperature range from -200°C to 200°C were studied with the help of

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Linkam temperature-controlled cell. As a result of thermal at 200°C, the luminescence intensity decreased but no maximum shift of the spectrum was observed, whereas returning to room temperature, the initial luminescence intensity values were restored. When the temperature drops to -200°C, the luminescence intensity of the sample increases, in this case the reaction is reversible.

The effect discovered can be used to create thermostable fluorescent marks, the physical size of which is limited by the diffraction resolution of the optics ( $\sim 200\text{-}300\text{ nm}$ ) used for exposure.

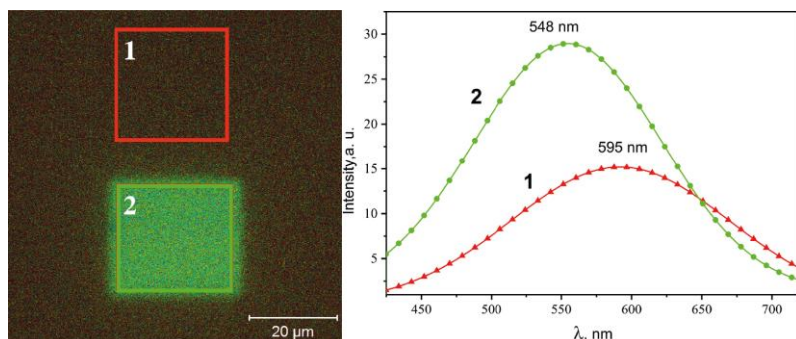


Fig.1. Fluorescence image (left) and luminescence spectrum (right) of the carbon dots film before (1) and after (2) 405nm laser exposure

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## **THE PRACTICAL APPLICATION OF MODERN QUANTUM TECHNOLOGIES IN BIOMEDICINE**

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Currently, biomedicine uses a large number of scientific perspective technologies [1]. First of all, it is quantum technologies. Their utilization allows us to solve actual problems in various fields of biomedicine. The modern quantum biomedical technologies such as quantum sensors, quantum computers and quantum communication lines will be considered. It will be shown that the use of modern technologies based on the latest advances in quantum physics can provide better patient care.

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**THE INFLUENCE OF TEMPERATURE ON  
BIODISTRIBUTION OF N,N,N',N'-  
ETHYLENEDIAMINETETRAKIS(METHYLENE  
PHOSPHONIC) ACID LABELED WITH GALLIUM-68**

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Many solid tumors are known to metastasize into bones. These bone metastases can induce various complications such as severe bone pain and pathological fractures [1]. Nowadays, positron emission tomography (PET) provides improved spatial resolution and lesion contrast as compared with other imaging techniques of bone metastases detection. Cyclotron produced <sup>18</sup>F-fluoride and <sup>18</sup>F-fluorodeoxyglucose have widely used as bone imaging agents, but they have high costs.

Alternative radionuclide for PET imaging is positron-emitting gallium-68. <sup>68</sup>Ga ( $T_{1/2} = 68$  min,  $\beta^+ = 89\%$ ,  $E_{\beta^+max} = 1.9$  MeV) can be produced on-site from <sup>68</sup>Ge/<sup>68</sup>Ga generator throughout 1 year. Phosphonates are ideal ligands for <sup>68</sup>Ga due to their high affinity to hydroxyapatite of bone tissue. In this study we synthesized three <sup>68</sup>Ga- N,N,N',N'-ethylenediaminetetrakis(methylene phosphonic) acid (<sup>68</sup>Ga-EDTMP) formulations at different temperature and evaluated their biodistribution.

All studies were carried out in intact healthy *Wistar* rats. The animals were divided at 3 equal groups. The rats of first groups were injected with 0.37 MBq in a volume 0.1 ml of <sup>68</sup>Ga-EDTMP prepared at room temperature. The rats of second and third groups were injected with 0.37 MBq of <sup>68</sup>Ga-EDTMP prepared at 50 °C and 95 °C, respectively, in a volume 0.1 ml. Animals were sacrificed at 5 min, 1, 2 and 3 h post-injection (p.i.), the samples of different organs and tissues were collected for gamma count. The uptake was expressed as percentage of inject-

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ed dose per gram of tissue (%ID/g). Also the total skeletal uptake was counted assuming the skeleton to be 10 % of the total body weight.

It was shown that temperature had an impact on skeletal uptake of  $^{68}\text{Ga}$ -EDTMP. Thus, the amounts of  $^{68}\text{Ga}$ -EDTMP prepared at 95 °C were higher as compared with the other formulations (Tab. 1). The peak concentration was  $34.38 \pm 1.20$  %ID at 1 h p.i., whereas the highest amounts of  $^{68}\text{Ga}$ -EDTMP prepared at 20 °C and 50 °C were  $22.34 \pm 2.12$  %ID and  $31.18 \pm 3.89$  %ID, respectively.

Table 1. Total amount of radioactivity in skeleton after intravenous injection of  $^{68}\text{Ga}$ -EDTMP prepared at different temperature (in % ID).

The data are presented as mean  $\pm$  standart error ( $M \pm m$ )

	Time after administration			
	5 min	1 h	2 h	3 h
$^{68}\text{Ga}$ -EDTMP (20 °C)	$15.52 \pm 2.53$	$21.88 \pm 0.45$	$22.34 \pm 2.12$	$20.36 \pm 4.17$
$^{68}\text{Ga}$ -EDTMP (50 °C)	$16.70 \pm 2.57$	$29.79 \pm 2.27$	$24.82 \pm 4.71$	$31.18 \pm 3.89$
$^{68}\text{Ga}$ -EDTMP (95 °C)	$25.72 \pm 1.67$	$34.38 \pm 1.20$	$32.01 \pm 2.79$	$27.98 \pm 4.36$

Among the soft tissue organs, the increasing temperature hadn't great impact on  $^{68}\text{Ga}$ -EDTMP biodistribution, but  $^{68}\text{Ga}$ -EDTMP prepared at 50 °C and 95 °C had slightly lower uptake than the other one.

In conclusion, all  $^{68}\text{Ga}$ -EDTMP formulations had high stability and predominantly bone tissue uptake. The growth of temperature affected  $^{68}\text{Ga}$ -EDTMP biodistribution in skeleton and slightly decreased amounts of activity in soft tissues and organs.

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## STUDY OF MECHANISMS INVOLVED IN THE RADIORESISTANCE OF HUMAN TUMOR CELLS

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Currently, radiation therapy is one of the main methods of the solid tumors treatment. The possible recurrence in long-term survivors after tumor treatment is associated with the occurrence of *de novo* or selection of already existing tumor cell clones that are resistant to ionizing radiation [1]. Clarification of the causes and mechanisms of this resistance, and at the same time, the search for ways to reduce it, remains an urgent task of experimental and clinical oncology and radiation biology for many years [2,3]. The aim of this study was to identify the characteristics of the formation of radioresistance of tumor cells at the molecular-cellular level.

In present study, the radioresistant clones of human tumor cells (A549 cell line) was obtained by X-rays acute treatment at a dose of 15 Gy (group “15 Gy”). A significant decrease in the residual foci of  $\gamma$ H2AX in cells of the “15 Gy” group compared with the “Control” group after the test-irradiation at a dose of 10 Gy was shown (Fig. 1).

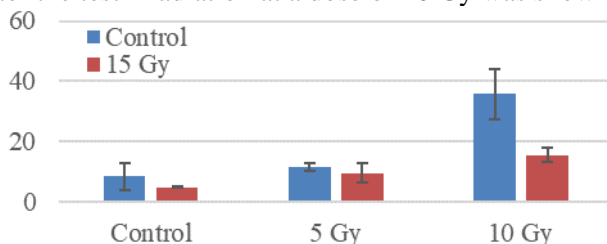


Fig.1. Number of residual foci of  $\gamma$ H2AX in different experimental groups

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A significant decrease in the number of micronuclei (MN) in the “15 Gy” group was revealed after additional exposure to X-rays at doses of 5 and 10 Gy compared to the cells of the “Control” group. Moreover, the number of cells containing three or more MN per cell is extremely low in “15 Gy” group (Table 1).

Table 1. Frequency of MN in A549 cells in different experimental conditions.

Dose (Gy)	0	1	2	3	>3	Total (cells)	MN	% MN
Control	481	17	1	1	0	500	22	4.4
0 + 5 Gy	246	100	71	37	34	488	489	100.2
0 + 10 Gy	149	41	43	30	37	300	365	121.7
15 Gy	493	6	1	0	0	500	8	1.6
15 + 5 Gy	402	73	24	0	0	499	121	24.3
15 + 10 Gy	387	64	37	7	5	500	179	35.8

According to the results obtained in three independent experiments to assess the ability of “Control” and “15 Gy” cells to form colonies, it was found that the clonogenicity of “15 Gy” group is significantly higher and confirms the data obtained by DNA residual  $\gamma$ H2AX foci and cytogenetic analysis, specifically, the ability of radioresistant cells to repair of lethal DNA damages more successfully.

Thus, one of the mechanisms determining the radioresistance of human tumor cells is their ability to repair of potentially lethal damages in genetic material more effectively.

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## CHARACTERIZATION OF THE GUT MICROBIOTA COMPOSITION WITH CHRONIC CONSTIPATION

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Chronic constipation (CC) is a prevalent gastrointestinal disorder with significant impact on patient's quality of life. Alterations of the gut microbiota have been suggested as a possible pathophysiologic mechanism of the disease [1]. Gut microbiota may affect intestinal motility via metabolites or end-products of bacterial fermentation, through the mediators released by the gut immune response, or intestinal neuroendocrine factors [2]. The aim of the present study is to characterize the composition of the gut microbiota of patients with CC and to identify microbes that are functionally active in relation to the motor-evacuation function of the intestine.

Fifteen colonic tissue samples were obtained from patients undergoing colectomy for CC. The mucosal microbiota was studied using culture-based and 16S rRNA pyrosequencing methods on the high-throughput Illumina MiSeq platform. The obtained sequences ~~for~~ were grouped into operational taxonomic units (OTU) based on the 97% similarity. Alpha- and beta-diversity parameters, such as the OTU number in the sample, Simpson, Chao1, and Shannon indices, were calculated to assess biodiversity and perform comparative community analysis. Beta-diversity was evaluated using the “unweighted” and “weighted” Unifrac algorithms followed by visualization by principal coordinate analysis (PCoA).

As a result, samples produced a total of 1,478,190 reads with an average of  $98,546 \pm 31,776$  reads per sample. An average of 460 OTUs were identified, with a minimum of 201 OTUs and a maximum of 592 OTUs. Analysis of biodiversity indices showed that for all samples, the

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obtained sequencing data were sufficient to cover the vast majority of prokaryotic species. Based on PCoA analysis, eight samples were grouped into a cluster, indicating phylogenetic similarity in the composition of their microbiota. However, beta-diversity analysis of the samples revealed absence of clustering by age and sex. The relation-between the anatomy of the colon and the composition of the intestinal microbiota was also not detected. Consequently, age, sex, and anatomy of the colon do not have a significant impact on the development of CC in patients.

The microbiota in constipated patients was dominated by bacteria belonging to the phyla *Firmicutes* (31-52%) and *Bacteroidetes* (34-43%), followed by *Proteobacteria* (4-26%) and *Actinobacteria* (1-4%). In CC patients we found an increased occurrence of the representatives of phyla *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*. Besides, the proportion of *Firmicutes* / *Bacteroidetes* was changed compared to healthy individuals. We identified no functional relation between the gut microbiota composition and CC, but identified some microbes which may affect motility via production of methane (*Methanobrevibacter*), hydrogen sulfide (*Desulfovibrio*, *Bilophila*, *Escherichia*, *Akkermansia*), butyrate (*Clostridiales*), propionate (*Bacteroides*, *Akkermansia*) and acetate (many taxa). Thus, our findings suggest a role for gut microbiota in constipation and promote a novel therapy strategy for constipation.

The study was performed by using the equipment of Interdisciplinary center for collective use of KFU for cellular, genomic and post-genomic research in Volga region and supported by Russian Foundation for Basic Research (grants 18-34-00268 and partly 18-415-160005 p\_a).

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## **MULTYPURPOSE CYCLOTRON FOR MEDICAL AND PHARMACEUTICAL PURPOSES**

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Among methods of treatment of oncological diseases proton therapy takes the unique place. Laid the foundation of proton therapy, William Bragg Sr. The point is that the proton at hit in a target at first almost does not lose energy, and then, before the stop, loses it very intensively. The curve received the name of a curve of Bragg, and the peak began to be called Bragg peak. Experiments with radiation of tumors a proton bunch began in Berkeley. For their receiving medical cyclotrons were used. Now in the world there are many centers of proton therapy.

Construction of the proton centers costs hundreds of millions dollars. Requirement them is very high. Main "instrument" of proton therapy — the accelerator of elementary particles, most often a cyclotron. Typical medical accelerators disperse protons to energy from 75 to 200 MEV. The possibility of receiving protons with different energy is important for therapy: they have Bragg peaks at the different penetration depth, forming thus the plateau of dozny distribution or the modified Bragg's peak (spread out Bregg peak, SOBP). Selecting the necessary distribution of protons for energy, it is possible "to fill" a tumor with ionization maxima evenly. The removed bunch of protons from the accelerator is transferred to the so-called medical room (treatment room, in the centers of their proton therapy usually from three to five) where there is a patient.

Cyclotrons are applied also in the pharmaceutical purposes to an operating time of isotopes for SPECT and PET. The pharmaceutical cyclotron can positively disperse also negatively charged ions to energy to 70 MEV.

In work the possibility of use of one cyclotron, both for medical, and for the pharmaceutical purposes is considered. At the same time the quantity of a gentra can be reduced, and advance of waiting list for treatment of patients can be accelerated. Besides modification of the existing cyclotrons for their use in the medical and pharmaceutical purposes is possible.

## **DYNAMICS OF THE TOTAL GLUTAMATE AND GLUTAMINE CONTENT IN RESPONSE TO A SHORT VISUAL STIMULUS IN VIVO**

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The aim of this study is to compare the dynamics of the Glx (total signal of glutamate and glutamine) and the BOLD signal.

Philips Achieva dStream 3T, SENSE Head-8 coil and InVivo SensaVue (for stimulus transmission) were used. 10 healthy subjects took part in the study. The 8 Hz flashing checkerboard was used for stimulation in similar blocks (3s - checkerboard, 21s -black screen).

EPI sequence was used with parameters: TR=3000 ms, NSA=120, the voxel size was 2.4×2.4×4mm<sup>3</sup>. The spectra were obtained using the PRESS sequence (TR=2000 ms, TE=35ms, NSA=864(12\*72), voxel size - 20x30x20mm<sup>3</sup>). The fMRI data were processed using the SPM12[1] software package. Statistical analysis of the images was performed using GLM. As a result, an activation map was obtained in response to visual stimulation. CBF obtained as the 1st core of the Voltaire series using a special algorithm in the SPM12 package[2].

Spectra were processed using LCmodel. For further statistical processing, the signal intensity ratios Glx/Cr were obtained. The difference between the obtained values between the spectra corresponding to individual time points was statistically determined by the Wilcoxon criterion.

A statistically significant difference in the ratio of Glx/Cr intensities between time points was revealed (fig.1). A correlation was found (r

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 =0.7113,  $p < 0.05$ ) between the ratio of the intensity values of the 1st and  
 23rd seconds and cerebral blood flow.

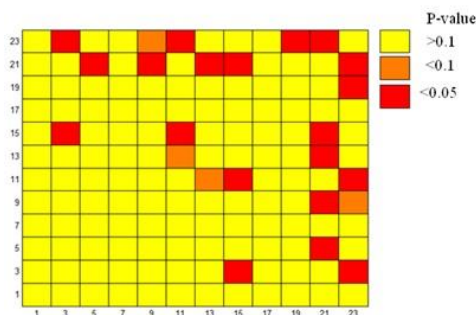


Fig. 1. A matrix showing the significance of differences between the ratio of intensities corresponding to two time points.

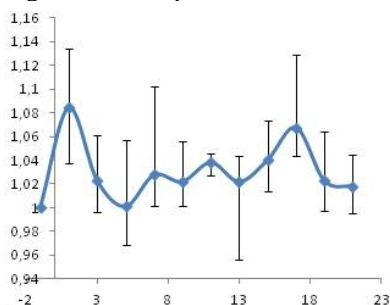


Fig. 2. The dynamics of the ratio Glx/Cr, normalized to 23 second intensity ratio. Dots mark the medians of the ratio, and the error bars show the 1st (bottom) and 3rd (top) quartiles.

Two periods of growth of the Glx were revealed, which indicates the activation of the glutamate-glutamine cycle twice per period. Correlation of the first peak of Glx growth with CBF may confirm the feedforward mechanism of the cascade of Glutamate induced hemodynamic response reactions.

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## ANALYSIS OF NANOPARTICLE UPTAKE IN LIVER BY MAGNETIC METHODS

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Targeted drug delivery by nanoparticles is the development of a  
theranostic paradigm in modern nanomedicine [1] and a step to high-  
tech and safe medicine of the future [2]. Understanding the pharmacoki-  
netic of nanoparticles is a milestone in these studies, as it determines not  
only the effectiveness, but also the safety of such therapy. The liver is  
known to be the main organ eliminating the nanoparticles bigger than 5  
nm diameter from the blood stream. However, due to the complex or-  
ganization of a living organism and many mutually affecting factors, it  
is impossible to study only interaction of particles with liver *in vivo*.

Here we offer a simple and convenient method based on perfusion  
model for studying pharmacokinetic of magnetic nanoparticles in the  
liver of laboratory animals (Fig.1). To detect magnetic particle concen-  
tration in the perfusate we used previously invented Magnetic Particle  
Quantification technique (MPQ) [3], which can measure nanoparticles  
concentration in wide range, non-invasively and in real-time [4,5].

We show that this model correctly describes the qualitative behavior  
of commercial and synthesized nanoparticles with various colloidal-  
chemical properties in the mice liver and can be used for further quanti-  
tative studies of pharmacokinetic nanoparticle properties.

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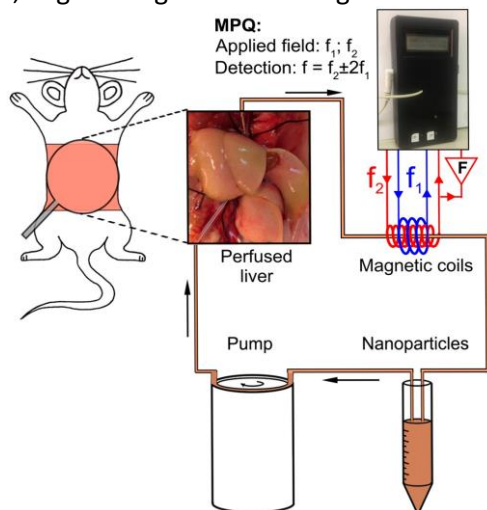


Fig.1. Experimental scheme of liver perfusion model for magnetic particle pharmacokinetics investigation (adapted from [4]).

### Acknowledgements

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### **3D IMAGE PROCESSING ALGORITHMS: AUTOMATIC EXTRACTION OF THE LEFT ATRIAL SEGMENT FROM THE RCT OF THE HUMAN RIB CAGE**

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**Key words:** Automation, Three-dimensional image processing, Atrial fibrillation treatment, RCT, Hounsfield Density.

**Description of the research:** The main idea of the project is isolation of the left atrium from the results taken on a computed tomography with the injection of contrast medium. During the research, the results of groups of patients were analyzed, statistical results were obtained, programs for working with histograms and their approximation were written, programs for detecting concentration contrast regions in different places of rib cage were written to obtain clear 3D model of the left atrium.

**Relevance:** Atrial Fibrillation becomes a dangerous pathology if not detected and eliminated the sources of origin in time. It can lead to heart attack and stroke in case of untimely treatment. The surgeon treats a heart by catheter ablation to prevent these serious pathologies.

There are no programs for automatic selection of the left atrial region from the results of CT scan today.

**Research methodology:** Based on CT scan results of twenty patients, a statistical range of contrast media densities was found on the Hounsfield scale. It belongs to the interval:  $x \in [168 \pm 36; 430 \pm 73]$ . Approximation by various functions was performed on this range. The Gauss function approximation was chosen on the course of the research, because time for post-processing of the 3D-image by the following algorithms is reduced when Gauss function approximation is used. Then an algorithm, exploring areas with zero contrast is used, and a contrast

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mask is obtaining. This distribution of the contrast of non-zero voxels allows automatically cut off the previously adjacent areas of the atrium by using the function "Remove unconnected areas" and get clear left atrium.

**The results:** The result of the work is a set of algorithms:

- For processing the obtained histograms
- For image processing in order to isolate the left atrium from them.

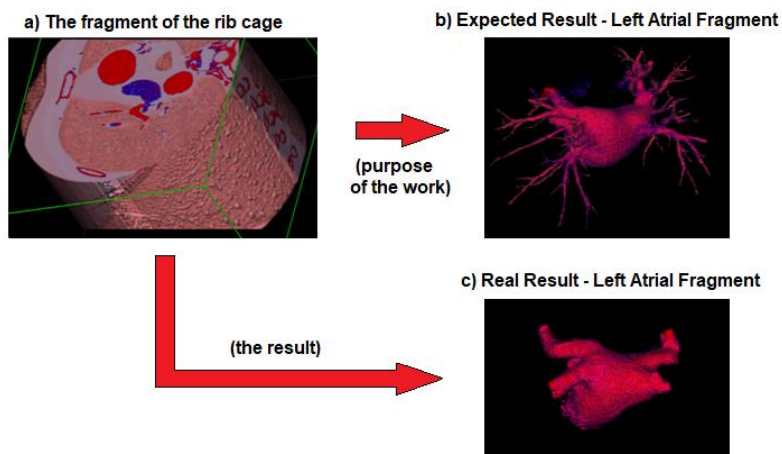


Fig.1. The purpose and the result of the research.

**Practical application of research results:** The developed programs and algorithms will be used in the software for equipment intended for the treatment of Atrial Fibrillation. The program will be able to speed up the work with the primary image, which is necessary during the operation.

**INFLUENCE PRESENCE OF DIVALENT IONS ON THE  
MORPHOLOGY OF GOLD NANOPARTICLES GENERATED  
BY LASER ABLATION OF SOLID TARGET IN WATER**

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In this work we investigate the formation of elongated gold nanoparticles, which occurred by laser ablation of gold target in aqueous solutions containing divalent ions ( $\text{CaCl}_2$ ,  $\text{BaSO}_4$ ,  $\text{MgSO}_4$ ,  $\text{Be}(\text{NO}_3)_2$ ) [1].

In all our experiments Ytterbium fiber laser (wavelength at 1060-1070 nm, pulse width of 200 ns, pulse repetition rate of 20 kHz, pulse energy of 1 mJ) was used as a radiation source. The peculiarity of our experiments is the use of additives of bivalent cations. The first experiments on irradiation of the gold target by laser ablation in liquid were carried out in water obtained by Milli-Q purification system with different concentration of calcium chloride ( $\text{CaCl}_2$ ). Extinction spectra show that a pronounced shift in the absorption maximum is observed with increasing concentration.

Results of the second part of experiments show that formation of elongated gold nanoparticles as chains is common process under laser ablation of the solid target in the presence of any divalent ions in water. TEM-image of a colloidal solution of gold nanoparticles at a concentration of  $\text{MgSO}_4$  in 1 mg/l is shown in Figure 1. The work discusses the mechanisms of formation of elongated nanoparticles by laser ablation of

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solids depending on the concentration of divalent ions in the liquid and the time of laser exposure [2].

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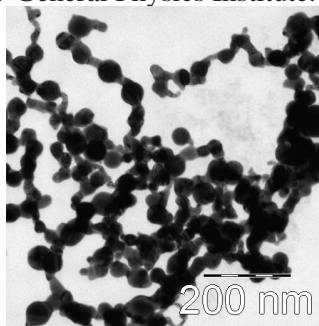


Fig.1. TEM-image of a colloidal solution of gold nanoparticles at a concentration of  $\text{MgSO}_4$  in 1 mg/l in water after laser irradiation of solid gold target.

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## DIAGNOSTIC IMAGING OF ACTIVATED LYMPHOCYTES IN VIVO DURING CELL IMMUNOTHERAPY OF CANCER PATIENTS

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Currently, malignant neoplasms are one of the most common causes of mortality. The lack of effective traditional methods of treatment is due to both late diagnosis and resistance of certain forms of cancer to the ongoing regimens of systemic therapy.

Over the past decades, significant progress has been made in the field of immunotherapy of oncological diseases, namely, the use of effector cells of innate immunity, in particular natural killers and T-lymphocytes, whose antitumor potential is enhanced by *in vitro* cultivation in the presence of cytokines [1]. This method has been developed and successfully implemented in clinical practice based on A. Tsyb Medical Radiological Research Center, it has shown a relatively high therapeutic efficacy in an integrated approach [2,3]. However, now there is no consensus on the key components of such therapy: how many cells (how and where) should be administered to the patient in order for such therapy to be crowned with objective success. Migration of activated human lymphocytes during intradermal injection have not been studied.

**The aim of the work** was to develop a technique for labeling of activated lymphocytes and their further visualization *in vivo* using SPECT / CT.

**Materials and methods.** The studied person was a patient diagnosed with breast cancer (T3N0M1), who received radical surgical treatment and chemotherapy; she also underwent accompanying immunotherapy with activated cytotoxic lymphocytes. Lymphocytes were isolated from the blood by the standard method, activated in a complete nutrient me-

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dium with the addition of IL-2, IL-15 and IFN-gamma for 3-5 days. Then selected activated lymphocytes were subjected to labeling with compound  $^{99m}\text{Tc}$ -THEOXIM. For detection of distribution of radiopharmaceutical reagent and labeled cells, the study was divided into three stages: 1) the injection of labeled non-activated cells; 2) the injection of pure radiopharmaceutical reagent; 3) the injection of labeled activated lymphocytes; for each stage, planar scintigraphy and a combined study of SPECT/CT were performed. The preparation and reagent were injected intradermal paravertebral at the level of the shoulder blades in two points, the break between injections was 7 days.

**Main results.** 1) the developed method of cell labeling (activity of 1 million cells – 2.0 MBq, viability – 95%) allowed to use them for imaging *in vivo* by SPECT/CT. 2) in the case of the injection of the patient labeled non – activated lymphocytes and pure radiopharmaceutical reagent on scintigrams can be observed hyperaccumulation of the reagent only in the places of their introduction, as well as the physiological accumulation of free reagent (kidneys, bladder, stomach), whereas the injection of labeled activated lymphocytes detected specific focus accumulation-axillary lymph node.

**Conclusion.** The study showed that labeled activated lymphocytes in the intradermal method of injection are deposited in the secondary organs of the immune system-lymph nodes, which are the place of their functioning, non-activated lymphocytes do not have this ability.

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**EFFECT OF ETHANOL ON THE TRANSPORT OF  
METHYLENE BLUE THROUGH THE RAT SKIN EX VIVO**

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Nowadays dyes are used in a wide class of medical supplies in optical methods of diagnostics, therapy and surgery. Methylene Blue (MB) is one of the most popular dyes used in medicine due to its biocompatibility, commercially, availability, safety and its fluorescence properties. [1-2] Nevertheless, despite of its popularity, diffusion of this dye through the skin has not been observed enough yet. The main goal of the study is to investigate the effect of ethanol aqueous solutions with volume concentrations 30, 40, and 50% on the transport of Methylene Blue (MB) in rat skin ex vivo.

Skin samples were taken from the hip area of white laboratory rats within an hour *postmortem*. Both hair and subcutaneous fat layers were thorough removed. Sample thickness was measured before and after MB solution penetration. MB was dissolved in aqueous 50%-, 40%-, 30%-ethanol solutions and in distilled water with a MB concentration 0.5 mg/mL.

Estimation of effective diffusion coefficient was performed on the base of measurement and analysis of skin diffuse reflectance under action of dye solution. More details of current work were performed in work [3].

Analysis of the differential absorbance ( $\Delta A$ ) kinetics has allowed evaluation of effective diffusion coefficient of MB (D) in skin and characteristic time ( $\tau$ ) of the dyeing process. Characteristic time corresponds to a relative change in the value of  $\Delta A$  in  $e$  folds.

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Values of the effective diffusion coefficient of the MB solutions have been evaluated as  $(1.85 \pm 0.06) \times 10^{-7} \text{ cm}^2/\text{c}$  in aqueous solution,  $(3.34 \pm 0.07) \times 10^{-6} \text{ cm}^2/\text{c}$ ,  $(3.04 \pm 0.07) \times 10^{-6} \text{ cm}^2/\text{c}$ , and  $(2.59 \pm 0.07) \times 10^{-6} \text{ cm}^2/\text{c}$  in 50%-, 40%-, and 30%-ethanol solutions, respectively. The average values of the characteristic time of skin samples dyeing have been evaluated as  $(24.6 \pm 4.42) \text{ min}$ ,  $(40.1 \pm 3.16) \text{ min}$ ,  $(46.8 \pm 2.7) \text{ min}$  and  $(79.4 \pm 11.92) \text{ min}$  in 50%-, 40%-, 30%-ethanol and aqueous solutions, respectively. Results of evaluation of the effective diffusion coefficient values have shown that addition of ethanol into the dye solution has led to a noticeable increase diffusion rate of the dye.

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## BIOSENSOR BASED ON POROUS SILICON

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**Abstract.** The object of this study is nanostructured composite systems based on porous silicon with glucose, tear and NaCl. The purpose of the work is to determine the possibility of manufacturing biomaterial based on porous silicon for a glucose sensor, for example, measuring the level of glucose in the blood. The electrical and optical properties of porous silicon and nanocomposites were studied. A study was conducted by IR spectroscopy of the composition of samples of porous silicon (PC) and nanocomposites: PC with glucose. A comparative analysis of the obtained results shows a noticeable difference between the IR spectra of nanocomposites and the IR spectrum of the initial porous silicon and allows one to identify the substance in the pores of PC.

*Keywords:* PC, glucose, nanocomposite, IR spectroscopy, biosensor.

One of the promising biomedical nanomaterials for various applications is porous silicon, which is a system of nanocrystals of various sizes and shapes, as well as porous silicon nanocomposites with various biological and inorganic substances [1].

A characteristic feature of porous silicon is the large total area of its inner surface. Depending on the value of porosity and pore geometry, it can be from 10 to 100 m<sup>2</sup> / cm<sup>3</sup> for macroporous silicon. The presence of a developed chemically active surface determines the possibility of porous silicon as a sensitive element of biosensors. In this paper, the possibility of using porous silicon as a material of glucose biosensor was investigated.

For various samples of porous silicon with NaCl; 1%, 2%, 3%, 4%, 5%, 6%, 10%, 12% glucose solutions measured current-voltage characteristics and calculated the conductivity in the dark and when illuminated with white light. During the experiment, it was found that the presence of glucose on the porous layer shows a significant increase in dark

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and light conductivity. The presence of NaCl in the sample does not significantly change the conductivity; the order remains the same.

A study of the surfaces, chips, and powders of samples of porous silicon and nanocomposite PC + glucose was carried out. The composition of the samples was studied by IR spectroscopy. The studies were carried out on the FSM 2201 using a diffuse reflection attachment and on a Perkin Elmer Spectrum 100 Fourier spectrometer using an attachment of impaired total internal reflection.

A study of IR spectroscopy of PC + glucose nanocomposites shows that the presence of glucose in the pores significantly changes the transmission spectra of the samples. Due to the presence of glucose, new transmission bands at 1847 nm, 2005 nm, 2669 nm appear on the spectra of porous silicon. To develop a PC-based material suitable for use in glucose biosensor, it is necessary to provide for the unification of the surface of the samples. From this we can conclude that porous silicon is a promising material for creating a glucose biosensor.

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## **COMPLEX STUDY OF PIPS-DOSIMETER RESPONSE FOR LOW-IONIZING RADIATIONS: PRELIMINARY RESULTS**

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Biological objects in a space flight are exposed to different components of space radiation. More than 90 % of the absorbed dose can be delivered with low-ionizing charged particles [1].

Semiconductor dosimeters-radiometers for example DB-8 [2] or Lyulin type [3], were used for the space radiation monitoring for many years. However, the rapid development of element base and semiconductor detector technologies made a challenge for developers of space radiation instruments.

In this paper the prototype of novel silicon dosimeter (Dose Rate Instrument – DRI, manufactured by SNIIP-Plus Co., Ltd., Russia) is presented for space radiation registration as energy deposition spectrometer. Signals from different particles produced in modern PIPS-detector (Passivated Implanted Planar Silicon) are discriminated by amplitude and recorded with 256-channel amplitude-digital converter (ADC). The results are saved in flash-memory in the form of energy deposition spectra (EDS) for every 60 seconds of measurement. Analysis of the EDS-data allows obtaining information on flux, dose rate and accumulated dose of incoming radiations in real time mode.

The DRI prototype was calibrated at the Heavy Ion Medical Accelerator in Chiba (HIMAC, NIRS-QST, Chiba, Japan) with 100 and 160 MeV protons (which constitute the main fraction of total proton flux at

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low-Earth orbit [4]) at different incident angles. DRI provided reliable flux measurements, which were controlled by HIMAC scintillation counter.

Additionally, a run of DRI on board commercial flight Tokyo-Moscow was performed to test the possibilities of low-ionizing space radiation monitoring at aviation altitudes [5].

Preliminary analysis of DRI response has demonstrated its reliability for the registration of low-ionizing radiations. DRI instrument can be used for routine dosimetry for aircrew and space crew members. However, additional calibration with heavier particles such as He, C and O are required.

This work was performed as part of joint research project with heavy ions at NIRS-QST HIMAC facility (18H376) and supported by NIRS-QST. Authors would like to express their highest gratitude to NIRS-QST Administration and HIMAC staff for their kind support throughout experiment. The DRI instrument was designed in cooperation with S.P. Korolev Rocket and Space Corporation «Energia» (Korolev, Moscow Region, Russia).

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## GLIOMA CELL INTERACTION WITH CARBON NANOTUBES

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Single-walled carbon nanotubes (SWCNT) are effectively used in developing new biosensors [1], in targeted delivering the biologically active substances and are promising drugs for non-invasive treatment of tumor cells, so-called photo-thermolysis of malignant tumors [2, 3]. The aim of the study was to investigate the short- and long-termed effects of SWCNT in complex with DNA (SWCNT-DNA) on C6 glioma cells. Short-length (100-250 nm) SWCNT were previously dispersed in DNA aqueous solutions using ultrasonification.

It has been revealed, that SWCNT-DNA do not influence the cell viability at concentrations of up to 10 µg/ml. SWCNT-DNA in nontoxic concentrations has been found to penetrate and accumulate in cells after 2 h of cells cultivation in the presence of the complexes and nanotube accumulation reaches the saturation point after 18 h of cells exposure to SWCNT. Using Raman microspectroscopy it has been shown that SWCNT complexes accumulate in cytoplasm as small agglomerates, do not permeate nuclei and remain in cells throughout 5-8 passages. Prolonged C6 cells cultivation in the presence of SWCNT-DNA complexes (10-15 µg/ml) led to the decrease in cells proliferative activity during the first 3 passages followed by its further recovery, causing, therefore, activation of cell stress adaptation mechanisms. Contrary, SWCNT-DNA at concentration of 1.5-3.0 µg/ml slightly stimulate cell proliferation that results in the increase of cell number in samples.

Simultaneous application of Raman microspectroscopy and confocal fluorescent microscopy shows that the process of SWCNT-DNA complexes penetration into cells is accompanied by the modification of actin

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cytoskeleton. During SWCNT accumulation F-actin in cytoplasm forms the coating over SWCNT agglomerates.

The resting membrane potential of C6 glioma cells exposed to SWCNT-DNA was measured using patch-clamp method. The significant decrease in plasma membrane potential was observed in 1-2 h with its further recovery in 18-24 h of cells interaction with nanotubes. After 24 h of cells exposure to SWCNT-DNA the value of resting membrane potential reaches the value of the membrane potential in control cells.

SWCNT-DNA were found to localize near mitochondria leading to the decrease of mitochondrial membrane potential in 18 h compared to that of control cells, initiate the increase in the production of superoxide, cause the changes in electron transfer in complexes I and III.

Our findings support the hypothesis of the SWCNT-DNA endocytosis by C6 glioma cells as the main mechanism of SWCNT uptake. In spite of modification of cellular metabolism by intracellular SWCNT-DNA accumulation and aggregation, C6 glioma cells proliferate distributing nanotubes between daughter cells. Thus, SWCNT-DNA complexes could be used for cancer theranostics.

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## PHOTOLUMINESCENT PROPERTIES OF SILICON NANOPARTICLES PREPARED FROM SILICON MONOXIDE

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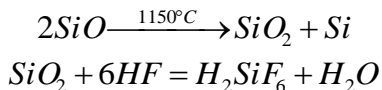
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Silicon nanoparticles (Si-NPs) are low cost and non-toxic and they exhibit interesting physical and chemical properties [1]. Furthermore, Si-NPs can be used in biomedicine, for example, in the form of biopolymer coated quantum dots for the diagnostics and therapy of cancer [2].

In our work Si-NPs were synthesized by the disproportionation reaction of silicon monoxide followed by etching in hydrofluoric acid [3]:



Since hydrosilylation leads to an increase in the intensity of photoluminescence (PL), the surface of Si-NPs was modified by 1-octadecene [4]. Also, this process provides significant possibilities for controlling the hydrophilicity of nanosilicon, eventually allowing them to dissolve in organic solvents. In our work, n-hexane was used.

PL was excited by using cw radiation of a laser diode at 450 nm with intensity below 10 mW/cm<sup>2</sup>.

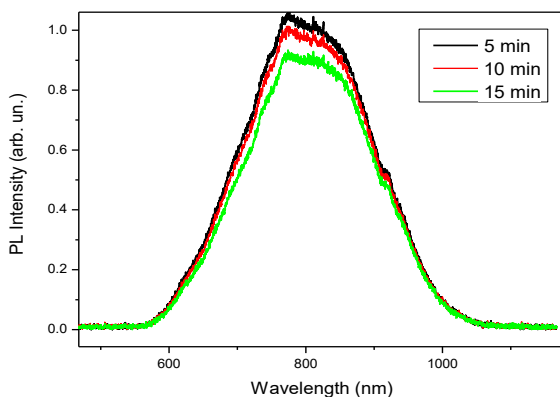


Fig.1. PL spectra of Si-NPs over time under laser irradiation.

The PL intensity of the obtained Si-NPs gradually decreased in air (see Fig. 1). For dried Si-NPs, this effect was much more noticeable. This problem can be solved by dissolving them in dextran.

The introduction of Si-NPs into the body in the form of a solution in n-hexane is unacceptable, therefore, the possibility of their dissolution in water should be investigated in further experiments.

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## **INCREASE IMAGE QUALITY OF X-RAY IMAGE SYSTEM ONYX**

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The goal of work is development and implementation of algorithms to increase quality of projection images on x-ray imaging system of radiation therapy complex Onyx. Different factors affecting on projection image quality – dark signal, lag effect, gain, bad pixel, scatter, geometry blur – were analyzed.

Several methods were developed to minimize negative factors and increase quality of projection images. Images were compared before and after correction via analysis of modulation transfer function, signal-to-noise ratio, and noise power spectrum

Correction of the dark signal increased the contrast ratio from 0.55 to 0.71 for 0.56 lp/mm. Gain correction increased signal-to-noise ratio by 1.3.

Scatter reduction using antiscatter grid increased contrast ratio of image, however, entailed radiation intensity increasing. Implementation of the grid with a ratio 1:12 increased contrast ratio from 0.22 to 0.39, and decreased signal-to-noise ratio from 60 to 40.

Deconvolution reduced effect of geometric blur in image, details with a higher spatial frequency became more distinguishable, boundaries of small objects were defined more clearly. On the other hand, deconvolution increased noise and artifacts, so that wrong contours of the structures appeared.

Correction and suppression of affecting factors can significantly improve quality of projection images. This allows enhancing the information and diagnostic properties of x-ray imaging system.

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