BIONANOTOX 2019

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10th INTERNATIONAL CONFERENCE

"BIOMATERIALS AND NANOBIOMATERIALS:

Recent Advances Safety-Toxicology And Ecology Issues

Including Russian-Hellenic Workshop And School Of Young Scientists

MAY 05-12, 2019, AGAPI BEACH, HERAKLION, CRETE - GREECE

HELLENIC SOCIETY OF TOXICOLOGY

M. SHEMYAKIN AND YU. OVCHINNIKOV INSTITUTE OF BIOORGANIC CHEMISTRY

UNIVERSITY OF CRETE

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AMPHION

D. MENDELEYEV UNIVERSITY OF CHEMICAL TECHNOLOGY OF RUSSIA

Final Program/Abstract Book

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INVITATION LETTER

On behalf of the organizing committee of 10th International Conference "Biomaterials and Nano-biomaterials: Recent Advances Safety – Toxicology and Ecology Issues" Including Workshop and School of Young Scientists and Symposium of Bio Nano-toxicology, we are privileged to invite you to grace with your presence and participation in the Conference, which is going to be held in Heraklion, in the beautiful island of Crete, Greece.

Crete is one of Europe's most popular holiday destinations. The island's historic importance as Knossos, Phaistos and Gortys is evidenced by thousands of visitors to these sites each year. Heraklion is located almost in the centre of Crete.

The main topic of Bionanotox Conference is Bio Nano-toxicology that lies on the interface of several scientific fields, such as biology, chemistry, toxicology, computational science chemistry, nanotechnology and biotechnology. The Conference is a continuation of a long term co-operation between scientists of these fields, which has been ongoing for the last 20 years, in the frame of the bilateral scientific state programs.

It is anticipated that scientists working in the most prominent Universities, Technological Institutes and Companies as well as distinguished field specialists coming from several countries will attend the Conference. Very low package fees including registration, accommodation, lunch meals and conference material have been secured for participants, in order to enable more young scientists to attend the Conference.

At Bionanotox Conference the attendee will have the chance to meet important representatives of research, discuss with them and exchange ideas. This will accomplish the aim of the Conference, which is the generation of new and vigorous interactions between the different aforementioned scientific fields leading to enormous positive effects in our societies.

Co-Chairmen of the Organizing Committee

Aristidis Tsatsakis, PhD, DSc, ERT

Mikhail Shtilman, PhD, DSc

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Ulbrich Karel	Professor, Head of Dept. of Biomedicinal Polymers, Institute of Macromolecular Chemistry, Prague, Czech Republic
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Vladimirov Yurii	Academician of RAS, Moscow State University
Volova Tatiana	Professor, Director of Department of Biotechnology, Siberian Federal University, Krasnoyarsk, Russia

COMMITTEES

Organizing Committee

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Co-President of the Conference	
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Tsakalof Andreas	Professor, Medical Chem. Dep., University of Thessaly, Larissa, Greece
Tzatzarakis Manolis	PhD, Assistant Professor, University of Crete, Iraklion, Greece
Velonia Kelly	Associate Professor, Department of Materials Science and Technology, University of Crete

Sunday, May 5, 2019

Arrival - Registration

20:00 ***WELCOME COCKTAIL***

Monday, May 6, 2019

08:00-09:30 **BREAKFAST**

10:00 **OPENING CEREMONY**

10:00-10:10 ***WELCOME ADDRESS***

Aristidis M. Tsatsakis, Co-chairman of Organizing Committee
University of Crete, Iraklion, Crete, Greece

10:00 **HONORED HOLY MONASTERY OF TOPLOU - MONASTERY OF PANAGIA AKROTIRIANI**

The Venerable Metropolitan (Bishop) of Ierapetra and Sitia, Kirillos (Diamantakis) and Achimandrite Theofilos, Superior of the Holy Monastery of Toplou or Monastery of Panagia Akrotiriani will be receiving the prize on behalf of the Holy Monastery

Honored for their long-term and continuous personal work, their spirituality and dedication to preserving the ecclesiastical art of Cretan and Russian origins and traditions, biological agriculture, environmental respect, as well as the worldwide tourist promotion and significant cultural development of the impressive, important, beautiful and historical fortress the Monastery of Toplou in the far Eastern part Crete.

10:10-10:20 **ABOUT SYMPOSIUM PROGRAM**

Mikhail I. Shtilman, Co-head of Organizing Committee
D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia

10:20-11:00 **ADVANCES IN ENGINEERING NANOSYSTEMS FOR DRUG DELIVERY**

Vladimir Torchilin, Honorary President of Conference
Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA 02115, USA

11:00-11:30 **COFFEE BREAK, *POSTER SESSION***

11:30-13:00 ***MORNING SESSION***

Chairmen: Prof V.P. Torchilin, Prof B.B. Dzantiev

11:30-12:00 **COMPARATIVE PHYSIOLOGY OF VISION: THE MECHNAISMS OF ADAPTATION OF INVERTEBRATE AND VERTEBRATE EYES TO LIGHT HABITAT; THE PROBLEM OF "LIGHT POLLUTION" FOR HUMANS**

M. A. Ostrovsky[1,2]
[1]N.M. Emanuel Institute of Biochemical Physics, Russian Academy of Scieneces
[2]Department of Molecular Physiology, Faculty of Biology, Lomonosov Moscow State University

12:00-12:30 **NEUROENZYMOLOGY – NEW CHALLENGES AND NEW SOLUTION**

S.D. Varfolomeev
Institute of Physical and Chemical Basics of the functioning of neuron networks and artificial intelligence, M. Lomonosov Moscow State University

Monday, May 6, 2019

12:30-13:00 **TARGETING CXCR4 WITH IMMUNO-MODIFIED IRON OXIDE NANOPARTICLES FOR CANCER TREATMENT WITH MAGNETICALLY-INDUCED HYPERTHERMIA**

V. Vilas-Boas[1,2], B. Espiña[2], Y.V. Kolen'ko[2], M. Bañobre-Lopez[2], J.A. Duarte[3], V.C. Martins, D.Y. Petrovykh[2], P.P. Freitas[2], and F. Carvalho[1]

[1]UCIBIO, REQUIMTE, Laboratory of Toxicology, Biological Sciences Department, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal

[2]International Iberian Nanotechnology Laboratory, Av. Mestre José Veiga, 4715-330 Braga, Portugal

[3]CIAFEL, Faculty of Sports, University of Porto, Rua Dr. Plácido da Costa 91, 4200-450 Porto, Portugal

13:00-16:30 **BREAK**

16:30-19:00 ***EVENING SESSION***

Chairmen: Prof N.L. Klyachko, Prof S.A. Eremin

16:30-16:55 **STUDY OF THE MECHANISM OF FREE RADICAL REACTIONS CATALYZED BY THE COMPLEX OF CYTOCHROME C WITH ANIONIC LIPIDS (CYT-AL) IN CELL MEMBRANES AND MITOCHODRIA**

G.K. Vladimirov[1,2], Yu.A. Vladimirov [1,2,3]

[1] Shubnikov Institute of Crystallography of Federal Scientific Research Centre "Crystallography and Photonics" of Russian Academy of Sciences", Moscow, Russia

[2] Laboratory of Navigational Redox Lipidomics, IM Sechenov Moscow State Medical University, Moscow, Russia

[3] Lomonosov Moscow State University, Moscow, Russia

16:55-17:20 **NEW NANOSCALE POLYMERIC SYSTEMS FOR ANTICANCER THERAPY**

A.L. Luss[1], P.P. Kulikov[1], A.N. Kuskov[1], A.V. Goryachaya[1], S.A. Gusev[2], M.I. Shtilman[1]

[1]D.Mendeleev University of Chemical Technology of Russia.

[2] Federal Research and Clinical Center for Physical-Chemical Medicine of Federal Medical Biological Agency, Moscow, Russia

17:20-17:45 **THERMAL, MECHANICAL AND BIODEGRADATION STUDIES OF BIOFILLER BASED POLY-3-HYDROXYBUTYRATE BIOCOMPOSITES**

E.G. Kiselev[1,2], S. Thomas[1,3]

[1]Siberian Federal University. Institute of Fundamental Biology and Biotechnology, Krasnoyarsk, Russia

[2]Institute of Biophysics SB RAS, Federal Research Center "Krasnoyarsk Science Center SB RAS", Krasnoyarsk, Russia

[1,3]International and Interuniversity Centre for Nano Science and Nano technology, University, Kottayam, Kerala, India

17:45-18:10 **SYNTHESIS OF PHAS BY HYDROGEN BACTERIA IN A PILOT PRODUCTION PROCESS**

A.V. Demidenko[1,2], Evgeniy Kiselev[1,2], Natalia Zhila[1,2], Tatiana Volova[1,2]

[1]Siberian Federal University, 79 Svobodnyi Av., Krasnoyarsk 660041, Russia

[2]Institute of Biophysics SB RAS, Federal Research Center "Krasnoyarsk Science Center SB RAS", 50/50 Akademgorodok, Krasnoyarsk 660036, Russia

Monday, May 6, 2019

18:10–18:30 **APPROACHES OF CANCER THERAPY BASED ON INDUCING OF APOPTOSIS AND FERROPTOSIS**

A.M. Nesterova[1,2], G.K. Vladimirov[1,2], A.A. Levkina[1,3], Yu.A. Vladimirov[1,4]
[1]Shubnikov Institute of Crystallography of Federal Scientific Research Centre "Crystallography and Photonics" of Russian Academy of Sciences, Moscow, Russia
[2]Institute for Regenerative Medicine Sechenov University, Moscow, Russia
[3]Pirogov Russian National Research Medical University, Moscow, Russia
[4]Lomonosov Moscow State University, Moscow, Russia

18:30–19:00 **DEVELOPMENT OF NEW IMPLANTABLE BONE GRAFTS WITH RHBMP-2 AND ERYTHROPOIETIN FOR RECONSTRUCTIVE SURGERY**

A.V. Gromov[1], F.S. Senatov[2], P.A. Orlova[1], T.M. Grunina[1], M.S. Poponova[1], N.V. Strukova[1], K.E. Nikitin, V.G. Lunin[1,3], A.S. Karyagina[1,3,4]
[1]Gamaleya Research Institute for Epidemiology and Microbiology, Moscow, Russian Federation
[2]National University of Science and Technology "MISIS", Moscow, Russian Federation.
[3]Institute of Agricultural Biotechnology, Moscow, Russian Federation
[4]A.N. Belozersky Institute of Physical and Chemical Biology, M.V. Lomonosov Moscow State University, Moscow, Russia

Tuesday, May 7, 2019

08:00–09:30 **BREAKFAST**

10:00–13:15 ***MORNING SESSION***

Chairmen: Prof A.M.Tsatsakis, Prof M.A.Ostrovskiy

10:00–10:30 **INFLUENCE OF ARYLOXYALKANOIC ACIDS DERIVATIVES ON SOIL MICROBIOCENOSIS**

V.N. Rakitskii, T.A. Sinitskaya, I.P. Gromova, G.M. Truhina
Federal Scientific Center of Hygiene named after F.F. Erisman, Moscow, Russia

10:30–11:00 **BIOASSAY ON THE BASE OF FUNCTIONALYZED NANOPARTICLES**

B.B. Dzantiev
A.N. Bach Institute of Biochemistry, Research Centre of Biotechnology Russian Acad. Sci., Moscow, Russia

11:00–11:30 **TRANSIENT INCOMPLETE SEPARATION FACILITATES FINDING ACCURATE EQUILIBRIUM DISSOCIATION CONSTANT, KD, OF PROTEIN–SMALL MOLECULE COMPLEX**

S. N. Krylov[1], N. Sisavath[1], J. L. Rukundo[1], J. C. Yves Le Blanc[2], V. A. Galievsky[1], J. Bao[1], S, Kochmann[1], A. S. Stasheuski[1]
[1]Department of Chemistry and Centre for Research on Biomolecular Interactions, York University, Toronto, Ontario M3J 1P3, Canada
[2]SCIEX, Concord, Ontario L4K 4V8, Canada

11:30–12:00 **SELECTION OF DNA APTAMERS BASED ON SEPARATION OF DNA–PROTEIN COMPLEXES FROM DNA LIBRARY USING DIFFERENT METHODS OF CAPILLARY ELECTROPHORESIS**

S.M. Krylova, An T.H. Le, S.N. Krylov
Department of Chemistry and Centre for Research on Biomolecular Interactions, York University, Toronto, Ontario M3J 1P3, Canada

Tuesday, May 7, 2019

12:00-12:15 **COFFEE BREAK, *POSTER SESSION***

Chairmen: Prof V.N.Rakitskii, Prof R.D.Katsarava

12:15-12:45 **SYNTHETIC OLIGOSACCHARIDES AND GLYCOCONJUGATES AS INDISPENSABLE TOOLS FOR THE DEVELOPMENT OF IEA DIAGNOSTIC KITS FOR THE DETECTION OF PG-AMOUNTS OF MICROBIAL POLYSACCHARIDES**

N.E.Nifantiev
Laboratory of Glycoconjugate Chemistry, N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, 119991 Moscow, Russia

12:45-13:15 **TOWARDS THE BIOFABRICATION OF HUMAN THYROID GLAND CONSTRUCTS: 3D CULTIVATION OF THYROCYTES, THYROID FOLLICLES, AND MICROORGANS**

N.S.Sergeeva[1,2], Yu.D.Khesuani[2,3], V.A.Kirsanova[1], P.A.Karalkin[1], I.K.Sviridova[1], A.P.Polyakov[1]
[1]P.A.Hertsen Moscow Oncology Research Center - branch of NMRRC, Moscow, Russia
[2]Pirogov Russian National Research Medical University, Moscow, Russia
[3]Private Laboratory for biotechnological research "3D Bioprinting Solutions", Moscow, Russia

13:15-16:30 **BREAK**

16:30-19:00 ***EVENING SESSION***

Chairmen: Prof E.A.Markvicheva, Prof Yu.I.Golovin

16:30-17:00 **LIPOSOMES FOR TARGETED ANTICANCER DRUG DELIVERY: SYNTHESIS AND EVALUATION IN 3D IN VITRO MODEL**

A. Gileva[1], A. Sapach[1], O. Koloskova[2], K. Vlasova[3], N. Klyachko[3], Yu.Golovin[4], E. Markvicheva[1]
[1]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia
[2]NRC Institute of Immunology FMBA of Russia, Moscow, Russia
[3]Moscow State University, Moscow, Russia
[4]G.R.Derzhavin Tambov State University, Tambov, Russia

17:00-17:30 **TOXIC EFFECTS OF THE FUNGICIDE TEBUCONAZOLE ON FUSARIUM-INFECTED WHEAT PLANTS**

N.G.Menzyanova
Siberian Federal University, 79 Svobodnyi Av., Krasnoyarsk 660041, Russia

17:30-18:00 **RECOMBINANT BACTERIOPHAGE ENDOLYSIN LYS394: LYSIS E.COLI UNDER ULTRALOW-FREQUENCY ALTERNATING MAGNETIC FIELD IN THE PRESENCE OF MAGNETIC NANORODS**

A.D. Usvaliev[1], E.P Sergeev[1], P.G. Rudakovskaya[5], S.L. Gribanovsky[3], A.O. Zhigachev[3], M.M. Veselov[1], K.A. Miroshnikov[4], S.A. Legotsky[1], E.A. Zaitseva[1], A.V. Finko[1], A.G. Majouga[5,2,1], Yu.I. Golovin[1,3], A.V. Kabanov[1,6], N.L. Klyachko[1,3,6]
[1]M.V. Lomonosov Moscow State University, Moscow, Russia;
[2]National University of Science and Technology "MISIS" (MISIS), Moscow, Russia;
[3]G.R. Derzhavin Tambov State University, Tambov, Russia;
[4]M.M. Shemyakin, Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia;
[5]D. Mendeleev University of Chemical Technology of Russia, Moscow, Russia,
[6]University of North Carolina, Chapel Hill, NC, USA

18:00-18:15	**COFFEE BREAK, *POSTER SESSION***
18:15-18:35	**CALIBRATED SPHERICAL MICROPARTICLES FOR EMBOLIZATION OF THE VASCULAR BED ON THE BASIS OF POLYVINYL ALCOHOL HYDROGELS** **L. A. Bryukhanov[1], A. A. Artyukhov[1], M.I. Shtilman[1]** *[1]Department of Biomaterials, D. Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation*
18:35-18:55	**MACROPOROUS POLYMERIC HYDROGELS FOR THE REGENERATION OF THE SPINAL CORD** **K.S. Kushnerev[2], A.A Artyukhov[2], M.I. Shtilman[2] , A. Dekopov[1], E. Salova[1], A. Piskareva[2], A.Tomskiy[1]** *[1]D.Mendeleyev University of chemical Technology of Russia, Moscow , Russian Federation* *[2]Burdenko Research Institute of Neurosurgery, Moscow , Russian Federation*

Wednesday, May 8, 2019

08:00-09:30	**BREAKFAST**
	Chairmen: Prof N.S.Sergeeva, Prof Sergey N. Krylov
10:00-10:30	**ANTIMICROBIAL PROFILING OF DIFFERENTLY SURFACE-FUNCTIONALIZED SELENIUM NANOPARTICLES** **A. Kahru[1,2], I. Kurvet[1], I. H. Vija[1], I. Vinkovic-Vrček[3], A. Selmani[4], R. Barbir[3], K. Kasemets[1]** *[1]National Institute of Chemical Physics and Biophysics, Laboratory of Environmental Toxicology, Tallinn, Estonia* *[2]Estonian Academy of Sciences, Tallinn, Estonia* *[3]Institute for Medical Research and Occupational Health, Zagreb, Croatia* *[4]Rudjer Boskovic Institute, Zagreb, Croatia*
10:30-11:00	**NEW BIODEGRADABLE FIBRILAR COMPOSITES ON THE BASE OF POLY(3-HYDROXYBUTYRATE) AND POLYLACTIDE FOR SELECTIVE PURIFICATION OF SEWAGES FROM OIL** **S.Z. Rogovina, A.L. Iordanskii, A.A. Berlin** *Semenov Institute of Chemical Physics of Russian Academy of Sciences, Russia*
11:00-11:30	**LIBRARY OF CATIONIC POLYMERS COMPOSED OF POLYAMINES AND ARGININE AS GENE TRANSFECTION AGENTS** **N. Zavradashvili[1], C. Sarisozen[2], G. Titvinidze[1], G. Otinashvili[1], T. Kantaria[1], D. Tugushi[1], J. Puiggali[3], V.P. Torchilin[2], R. Katsarava[1]** *[1]Institute of Chemistry and Molecular Engineering, Agricultural University of Georgia, Kakha Bendukidze University Campus, # 240 David Aghmashenebeli Alley, 0131, Tbilisi, Georgia* *[2]Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, 360 Huntington Ave., 02115, Boston, MA, USA* *[3]Universitat Politècnica de Catalunya, Av.Diagonal 647, Barcelona E-08028, Spain*
11:30-11:45	**COFFEE BREAK, *POSTER SESSION***
	Chairmen: Prof S.Z. Rogovina, Prof A.A. Berlin
11:45-12:15	**CHITOSAN-BASED BIOSORBENTS: MODIFICATION AND APPLICATION FOR SORPTION OF HEAVY METALS, DYES AND RADIONUCLIDES** **N.R. Kildeeva[1], G.R. Ulyabaeva[1,2], E.A. Podorozhko[2], S.N.Mikhailov[3], V.I. Lozinsky[2]** *[1]A.N. Kosygin Russian State University, Moscow, Russia* *[2]Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russia* *[3]Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia*

Wednesday, May 8, 2019

12:15-12:45 **MECHANISMS OF CROSS-LINKING OF CHITOSAN WITH ALDEHYDE DERIVATIVES**

S.N. Mikhailov[1], N.R. Kil'deeva[2]
[1]Engelhardt Institute of Molecular Biology, RAS, Vavilov St 32, Moscow , Russia;
[2]A.N.Kosygin Russian State University, Sadovnicheskaya St 33/1, Moscow , Russia.

12:45-16:30 **BREAK**

16:30-18:00 ***EVENING SESSION***

Chairmen: Prof E.A.Markvicheva, Prof Yu.I.Golovin

16:30-17:00 **ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) WITH PHOTOMETRIC AND CHEMILUMINESCENT DETECTION OF FUNGI**

Yu.S. Lebedin[1], Eu.S. Kostrikina[1], S.A.Eremin[2]
[1]XEMA Company Limited, 105264 Moscow, 9 Parkovaya str., 48, Russia
[2]M.V. Lomonosov Moscow State University, 119991 Moscow, Leninskie Gory 1, Russia

17:00-17:30 **CHITOSAN-BASED SCAFFOLDS FOR TISSUE ENGINEERING : PREPARATON AND IN VITRO EVALUATION**

T. Balabanova[1], A. Salnikova[2], M. Drozdova[1], N. Sazhnev[3], T. Demina[4], N. Kildeeva[3], E. Markvicheva[1]
[1]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Rus. Acad. Sci., Moscow, Russia
[2]D. Mendeleev University of Chemical Technology of Russia, Moscow, Russia
[3]A.N. Kosygin Russian State University, Moscow, Russia
[4]Enikolopov Institute of Synthetic Polymer Materials, Rus. Acad. Sci., Moscow, Russia

17:30-18:00 **LYSOSOMAL DELIVERY OF THE ENZYME, TTP1, LOADED IN EXTRACELLULAR VESICLES AND ITS ENHANCED DISTRIBUTION TO THE BRAIN IN THE ANIMAL MODEL OF BATTEN DISEASE**

N. L. Klyachko[1,2,3], M. J. Haney[1], E. B. Harrison[1], Y. Zhao[1], A.V. Kabanov[1,2], E. V. Batrakova[1]
[1]Center for Nanotechnology in Drug Delivery and Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[2]Deparment of Chemical Enzymology, Faculty of Chemistry, Lomonosov Moscow State University, Moscow, Russia
[3]G.R. Derzhavin Tambov State University, Tambov, Russia

Thursday, May 09, 2019

08:00-09:30 **BREAKFAST**

Chairmen: Prof O.A.Legonkova, Prof A.N. Kuskov

10:00-10:30 **TOXICITY OF DIFFERENTLY SIZED AND SURFACE-FUNCTIONALIZED SILVER NANOPARTICLES TO YEAST SACCHAROMYCES CEREVISIAE**

K. Kasemets[1], H. Vija[1], P. Mantecca[2], A. Kahru[1]
[1]National Institute of Chemical Physics and Biophysics, Laboratory of Environmental Toxicology, Tallinn, Estonia
[2]Department of Earth and Environmental Sciences, Research Centre POLARIS, University of Milano-Bicocca University, Milano, Italy

Thursday, May 09, 2019

10:30-11:00 **ANTIBACTERIAL METAL-BASED NANOPARTICLES: TOXICITY, MECHANISMS AND SAFETY TO HUMAN CELLS**

O. Bondarenko, A. Ivask, K. Kasemets, AL. Kubo, G. Vasiliev, A. Kahru
Laboratory of Environmental Toxicology, National Institute of Chemical Physics and Biophysics, Tallinn, Estonia

11:00-11:30 **BAYESIAN NETWORKS APPLICATION FOR THE PREDICTION OF CELLULAR EFFECTS FROM GENOME-WIDE TRANSCRIPTOMICS STUDIES OF EXPOSURE TO NANOPARTICLES.**

I.Furxhi, F. Murphy
Dept. of Accounting and Finance, Kemmy Business School, University of Limerick, Ireland. V94PH93

11:30-11:45 **COFFEE BREAK, *POSTER SESSION***

12:45-16:30 **BREAK**

11:45-12:15 **AMPHIPHILIC POLY-N-VINYLPYRROLIDONE NANOPARTICLES FOR MEDICAL APPLICATIONS: INTERACTION WITH BLOOD COMPONENTS *IN VITRO***

A.N. Kuskov[1,2], A.V. Goryachaya[1], P.P. Kulikov[1], A.L. Luss[1], M.I. Shtilman[1]
[1]Department of Biomaterials, D.Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047, Moscow, Russia
[2]Department of Technology of Chemical Pharmaceutical and Cosmetic Products, D.Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047 Moscow, Russia

12:15-12:45 **DEVELOPMENT OF 3D IN VITRO TUMOR MODELS FOR ANTICANCER DRUGS TESTING**

R.Akasov[1,2,3], A.Vaneev[4,5], A.Alova[4], O.Ryabaya[6], A.Garanina [1], A.Erofeev[1,4], P.Gorelkin [7], Y. Korchev [8,9], E.Markvicheva [3], A.Majouga [1,4,10]
[1]National University of Science and Technology «MISiS», Moscow, Russia
[2] M. Sechenov First Moscow State Medical University, Moscow, Russia
[3]Shemyakin Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russia
[4] Lomonosov Moscow State University, Moscow, Russia
[5] NanoProfiling Limited, Skolkovo Innovation Center, Moscow, Russia
[6] Blokhin National Medical Research Center for Oncology, Moscow, Russia
[7]Medical Nanotechnology LLC, Skolkovo Innovation Center, Moscow, Russia
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[10]D.Mendeleev University of Chemical Technology of Russia, Moscow, Russia

16:30-19:00 ***EVENING SESSION*** ***HALL 1***

Chairmen: Prof V.I.Shtilman, Prof T.G.Volova

16:30-17:00 **GEEN «BIOPLASTICS» IN SOLVING THE GLOBAL PROBLEM OF A POLYETHYLENE DUMP**

T.G. Volova
Siberian Federal University, 79 Svobodnyi Av., Krasnoyarsk 660041, Russia
Institute of Biophysics SB RAS, Federal Research Center "Krasnoyarsk Science Center SB RAS", 50/50 Akademgorodok, Krasnoyarsk 660036, Russia

Thursday, May 09, 2019

17:00-17:30 **MODIFIED COPOLYMERS OF MALEIN ANHYDRIDE WITH DIFFERENT FUNCTIONAL ACTIVITY**

G.I. Boyko[1], N.P. Lyubchenko[1], R.G. Sarmurzina[2], U.S. Karabalin[2], D.S. Tiesov[3], R.F. Mukhamedova[1], S.A. Taukeleva[4]
[1]Kazakh National Research Technical University named after KI Satpayev, Almaty, Kazakhstan
[2]Association «Kazenergy», Astana, Kazakhstan
[3]AO «Kazakhstan Petrochemical Industries», Astana, Kazakhstan
[4]Almaty State Institute of Advanced Medical Studies, Almaty, Kazakhstan

17:30-18:00 **AMPHIPHILIC OLIGOMERS OF ACRYLIC ACID AS CARRIERS OF WATER-INSOLUBLE BIOLOGICALLY ACTIVE SUBSTANCES**

Ya.O. Mezhuev[1], V.T. Dzhedzheya[1], O.Yu. Sizova[1], A.L. Luss[1], M.I. Shtilman[1], A.M. Tsatsakis[2]
[1]D. Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation
[2]University of Crete, Heraklion, Greece

18:00-18:30 **SCREENING OF BIOPOLYMERIC MATERIALS FOR CARDIOVASCULAR SURGERY TOXICITY—EVALUATION OF THEIR SURFACE RELIEF WITH ASSESSMENT OF MORPHOLOGICAL ASPECTS OF MONOCYTE/MACROPHAGE POLARIZATION IN ATHEROSCLEROSIS PATIENTS**

E.I.Shishatskaya[1], N.G.Menzyanova[1], D.P.Stolyarov[2], D.B.Dryganov[2]
[1]Siberian Federal University, 79 Svobodnyi Av., Krasnoyarsk 660041, Russia
[2]Federal Center for Cardiovascular Surgery, 45 Karaulnaya, Krasnoyarsk, 660020, Russia

16:30-17:10 **NEUROSOME ROUND TABLE DISCUSION** ***HALL 2***

Prof A. Tsatsakis, Prof D.A. Sarigiannis, Prof S. Karakitsios, Prof X. Coumoul, Prof I. Petridis, Prof J. O. Grimalt, Prof B. Tine

17:10-18:40 **SHORT ORAL PRESENTATIONS**

Chairmen: Prof A. Tsatsakis, Prof D.A. Sarigiannis

17:10-17:20 **TOXICITY OF GOLD NANOPARTICLES IN 4T1 AND A2780 PGL451 CELL LINES**

K. Sikorska[1], S. Męczyńska-Wielgosz[1], M. Wojewódzka[1], L. Kapka-Skrzypczak[2,3], M. Kruszewski[1,2,3]
[1]Institute of Nuclear Chemistry and Technology, Centre for Radiobiology and Biological Dosimetry, Dorodna 16, 03-195 Warsaw, Poland
[2]Institute of Rural Health, Department of Molecular Biology and Translational Research, Jaczewskiego 2, 20-090 Lublin, Poland
[3]University of Information Technology and Management, Department of Medical Biology and Translational Research, Sucharskiego 2, 35-225 Rzeszów, Poland

17:20-17:30 **ADVANCED ROUTINES IN THE ESTIMATION OF TELOMERE LENGTH USING BIOTEL**

I. Tsatsakis[1], P. Fragkiadaki[1], A. Alegakis[1], E. Vakonaki[1], M. Tzatzarakis[1], V. Karzi[1], E. Renieri[1], E. Sarandi[2], D. Tsoukalas[2], A. Tsatsakis[1]
[1]Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, Heraklion, Greece.
[2]Metabolomic Medicine, Health Clinics for Autoimmune and Chronic Diseases, Athens, Greece.

17:30-17:40 **IN VITRO ENDOTHELIUM COMPATIBILITY OF AMPHIPHILIC POLY-N-VINYLPYRROLIDONE NANOPARTICLES**

G. Fanouraki, A.Berdiaki, E. Perisynaki, A. Stratidakis, A. Kuskov, A. Tsatsakis, G. Tzanakakis, D. Nikitovic
Medical School, University of Crete

Thursday, May 09, 2019

17:40-17:50 **RISK ASSESSMENT OF EDCS IN EUROPE BASED ON HUMAN BIOMONITORING DATA**

S. Karakitsios[1,2], R. Razaee[1,2], D. Sarigiannis[1,2,3]
[1]HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, Greece
[2]Aristotle University of Thessaloniki, Department of Chemical Engineering, Environmental Engineering Laboratory, Thessaloniki, Greece
[3] School for Advanced Study (IUSS), Science, Technology and Society Department, Pavia, Italy

17:50-18:00 **EXPOSURE TO ENDOCRINE DISRUPTORS: URINARY PHTHALATE METABOLITE CONCENTRATIONS IN THE SLOVENIAN GENERAL POPULATION**

A. Runkel[1,2], J. Snoj Tratnik[1,2], D. Mazej[1], M. Horvat[1,2]
[1] Jožef Stefan Institute, Jamova cesta 39, 1000 Ljubljana, Slovenia
[2]Jožef Stefan International Postgraduate School, Jamova cesta 39, 1000 Ljubljana, Slovenia

18:00-18:10 **REAL LIFE RISK SIMULATION OF EXPOSURE TO ENDOCRINE DISRUPTORS**

V. Karzi[1], M. Tzatzarakis[1], E. Vakonaki[1], P. Stivaktakis[1], A. Kalliantasi[1], E. Apalaki[1], C. Chalkiadaki[1], M. Panagiotopoulou[1], I. Fragkiadoulaki[1], A. Tsatsakis[1]
[1]Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, Heraklion, Greece

18:10-18:20 **IMMUNODIAGNOSTIC DETERMINATION OF GLYPHOSATE IN WINE AND WATER SAMPLES**

V. Karzi[1], S. Daskalaki[1,2], M. Tzatzarakis[1], E. Iatrou[1], E. Vakonaki[1], S. Papachristou[1], E. Iliaki[1], A. K. Rizos[2], A. Tsatsakis[1]
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[2]Department of Chemistry, University of Crete and Foundation for Research and Technology - Hellas (FORTH-IESL), Heraklion, Greece

18:20-18:30 **QUALITY ASSESSMENT OF OMEGA-3 DIETARY SUPPLEMENTS IN THE GREEK MARKET**

N. Saliaj[1,2], M. Tzatzarakis[2], V. Karzi[1], E. Vakonaki[1], C. Giannakoudakis[1], A. K. Rizos[1], A. Tsatsakis[2]
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[2]Laboratory of Toxicology and Forensic Sciences, Medical School, University of Crete, Heraklion, Greece

18:30-18:40 **DEVELOPMENTAL EXPOSURE TO HEAVY METAL MIXTURE: NEUROBEHAVIORAL ANALYSIS IN AN IN VIVO MODEL**

Ö.Dinçkol, L.Ricceri, G.Calamandrei
Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy

Friday, May 10, 2019

08:00-09:30 **BREAKFAST**

16:30-18:00 ***MORNING SESSION NEUROSOME***

Chairmen: Prof D. Sarigiannis, Prof S. Karakitsios

10:00-10:30 **NEUROTOXICITY TESTING FOR PESTICIDES MIXTURES: RESEARCH APPLICATIONS AND REGULATIONS UNDER RLRS CONCEPT**

M. Goumenou
Department of Toxicology and Forensic Sciences of the Medical School at the University of Crete, Heraklion, Crete, Greece

Friday, May 10, 2019

10:30-11:00 — **EXPOSURE MODELLING AND EXPOSURE RECONSTRUCTION FOR CADMIUM**

I. Petridis
Aristotle University of Thessaloniki

11:00-11:30 — **RISK ASSESSMENT OF EDCS IN EUROPE BASED ON HUMAN BIOMONITORING DATA**

S. Karakitsios
Aristotle University of Thessaloniki

11:30- 12:00 — **NEUROSOME ESR 7: THE SCIENCE TO POLICY INTERACTION – DIFFERENT NEEDS OF DIFFERENT STAKEHOLDERS**

T. Bizjak
Jožef Stefan Institute

12:00 - 12:30 — **MERCURY CONCENTRATIONS IN EDIBLE FISH FROM THE WESTERN MEDITERRANEAN SEA (BALEARIC ISLANDS AND MARSEILLE)**

M. Capodiferro[1], E. Junque[1], E. Marco[1], R.M. Llull[2], J.O. Grimalt[1]
[1]Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Barcelona, Catalonia, Spain
[2]General Direction of Public Health and Consumption. Ministry of Health, Family and Social Welfare, Government of the Balearic Islands, Palma, Mallorca, Spain

12:30 - 13:00 — **BIOMONITORING OF LEAD IN A CHILDREN'S COHORT**

B. Fuentes[1], F. Ruggieri[1], O. Senofonte[1], A. Pino[1], S. Caimi[1], A. Nadiradze[2], T. Ugulava[2], L. Sturua[3], N. Gabriadze[3], A. Alimonti[1]
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13:00-16:30 — **BREAK**

16:30-18:00 — ***EVENING SESSION NEUROSOME***

Chairmen: Prof J. O. Grimalt, Prof T. Bizjak, Prof X. Coumoul

16:30-17:00 — **HIGH DIMENSION BIOLOGICAL ANALYSIS OF EARLY LIFE CO-EXPOSURE TO PLASTICIZERS AND METALS**

D. Sarigiannis
Aristotle University of Thessaloniki

17:00- 17:30 — **THE SH-SY5Y NEUROBLASTOMA CELL LINE AS A MODEL TO EVALUATE THE EFFECTS OF ENVIRONMENTAL POLLUTANTS ON NEURODEVELOPMENT**

L. Lopez-Suarez, C. Chauvet, X. Coumoul
Université Paris Descartes-INSERM UMR-S 1124, Paris, France

17:30-17:40 — **INTEGRATIVE AND CUMULATIVE HEALTH RISK FROM XENOBIOTICS EXPOSURE**

S. Karakitsios[1,2], V. Kokaraki[3], A. Gotti[3,4], D.A. Sarigiannis[1,2,3]
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[3] School for Advanced Study (IUSS), Science, Technology and Society Department, Pavia, Italy
[4] EUCENTRE Foundation, Pavia, Italy

Friday, May 10, 2019

17:40-17:50 **ADVERSE OUTCOME PATHWAYS ACTIVATED FROM EXPOSURE TO FLAME RETARDANTS AND CADMIUM**

S. Karakitsios[1,2], A. Stratidakis[3], D. Sarigiannis[1,2,3]
[1]HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, Greece
[2]Aristotle University of Thessaloniki, Department of Chemical Engineering, Environmental Engineering Laboratory, Thessaloniki, Greece
[3]School for Advanced Study (IUSS), Science, Technology and Society Department, Pavia, Italy

17:50- 18:00 **DEVELOPMENT AND IN VITRO CYTOTOXICITY OF AMPHIPHILIC POLY-N-VINYLPYRROLIDONE NANOPARTICLES CARRYING INDOMETHACIN**

S.E. Maravgaki[1], A.K. Stratidakis[1,2], M.N. Tzatzarakis[1], I. Tsatsakis[1], A.V. Goryachaya[3], P.D. Stivaktakis[1], A. Berdiaki[4], D. Nikitovic[4], M.I. Shtilman[3], A.K. Rizos[5], A.N. Kuskov[3,6], M.K. Tsilimbaris[7], A.M. Tsatsakis[1,3,6]
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CLOSING CEREMONY

Farewell Address – Closing Remarks

Saturday, May 11, 2019

08:00-09:00 **BREAKFAST**

10:00-13:00 **EXCURSION TO KNOSSOS PALACE**

Sunday, May 12, 2019

08:00-09:00 **BREAKFAST**

DEPARTURE OF PARTICIPANTS

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P 01 **APPLICATION OF CHITOSAN-POLYVINYL ALCOHOL FILMS FOR THE CONTROLLED RELEASE OF MEXIDOLE**

E.O. Batyrbekov[1], M.B. Umerzakova[1], Z.T.Utelbaeva[2]
[1]Institute of Chemical Sciences, Almaty, Kazakhstan
[2]Kazakh National Medical University, Almaty, Kazakhstan

P 02 **RELEASE BEHAVIOR OF FLUOROURACIL FROM CHITOSAN-COATED CALCIUM ALGINATE MICROPARTICLES**

E.O. Batyrbekov, M.B. Umerzakova
Institute of Chemical Sciences, Almaty, Kazakhstan

P 03 **MODIFICATION OF THE POLYSACHHIRIDE CAPSULES BY SILANIZATION**

A.S. Burova[1,2], D.B. Trushina[2,3,4], T.V. Bukreeva[2,4], T.N. Borodina[2,3]
[1] Lomonosov Moscow State University, Moscow, Russia
[2] Shubnikov Institute of Crystallography of Federal Scientific Research Centre "Crystallography and Photonics" of Russian Academy of Sciences, Moscow, Russia
[3] Institute of Molecular Medicine Sechenov First Moscow State Medical University, Moscow, Russia
[4] National Research Centre "Kurchatov Institute", Moscow, Russia

P 04 **THE USE OF MACROPOROUS POLYMER HYDROGEL BASE ON POLYVINYL ALKOHOL IN THE TREATMENT OF EXTENSIVE SOFT TISSUE DEFECTS AFTER ABDOMINALPERINEAL EXCISION**

S.M.Chudnykh[1], D.E.Kovalenko[1], A.A.Artyukhov[2]
[1]Moscow Clinical and Scientific Center, Moscow Healthcare Department, Moscow, Russia.
[2]D.Mendeleyev University of chemical technology of Russia, Moscow, Russia.
This work was supported by Russian Foundation to Basic Research 18-29-18039

P 05 **THE INFLUENCE OF SYNTHETIC STRATEGY ON THE POLY(4-OXYBENZOYL) PROPERTIES**

T.R. Deberdeev, E.K. Ignat'yeva, A.I. Akhmetshina, L.K. Karimova, S.V. Grishin, N.R. Galikhmanov, R.Ya. Deberdeev
Kazan National Research Technological University, Kazan, Russia

P 06 **WATER-SOLUBLE POLYMERIC FORMS OF PLANT GROWTH REGULATORS**

V.T. Dzhedzheya, M.A. Atabaeva, A.L. Luss, A.A. Dobrynin, M.S. Ustinova, M.I. Shtilman
D.Mendeleyev University of Chemical Technology of Russia, Moscow, Russian Federation

P 07 **THE INFLUENCE OF THE SIZE AND SURFACE CHARGE DENSITY OF LIPOSOMES ON THE PROPERTIES OF THEIR COMPLEXES WITH A MICROGEL**

G.K. Bozarova[1], O.V. Ivashkov[2]
[1]Department of Biomaterials, D. Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation
[2]M. V. Lomonosov Moscow State University, 119991 Moscow, Russia

P 08 **SYNTHESIS OF ANTI-TUBERCULOSIS DRUGS ENCAPSULATED FORMS**

D.A. Dynda, A.L. Luss, Ya.O. Mezhuev, M.I. Shtilman.
D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russian Federation

P09 **SYNTHESIS OF SMART HYDROGELS BASED ON COPOLYMER OF ALLYL GLYCIDYL ETHER AND N-VINYL PYRROLIDONE MODIFIED WITH DOPAMINE**

A.V. Varankin, Ya.O. Mezhuev, Yu.V. Korshak, M.I. Shtilman
D. Mendeleev University of Chemical Technology of Russia, Moscow, Russia

P10 **POLYMERIC METAL COMPLEXES**

A.L.Luss, E.A. Donskov, P.P. Kulikov, A.V. Goryachaya, M.A.Shirinkina, M.A. Atabaeva, M.S. Ustinova, G.I.Kandelaki
D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia

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P 11 POLY(VINYL ALCOHOL) + BACTERIAL NANOCELLULOSE + AG COMPOSITE CRYOGELS

T.M. Razheva[1,2], E.A. Podorozhko[2],A.G. Aslanli[3]

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This work was supported by Russian Foundation to Basic Research 18-29-18039

P 12 TOXICITY OF SILVER NANOPARTICLES IN 4T1 AND A2780 CELL LINES.

S. Męczyńska-Wielgosz[1], K. Sikorska[1], M. Wojewódzka[1], L. Kapka-Skrzypczak[2,3], M. Kruszewski[1,2,3]

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[2]Institute of Rural Health, Department of Molecular Biology and Translational Research, Jaczewskiego 2, 20-090 Lublin, Poland

[3]University of Information Technology and Management, Department of Medical Biology and Translational Research, Sucharskiego 2, 35-225 Rzeszów, Poland

P 13 OXIDATIVE POLYMERIZATION IN THE SYNTHESIS OF BIOCOMPATIBLE MATERIALS

Ya.O. Mezhuev[1], A.V. Varankin[1], I.V. Plyushchii[1], Yu.V. Korshak[1], P.G.Rudakovskaya[1], A.M. Tsatsakis[2]

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[2]University of Crete, Heraklion, Greece

P 14 MAGNESIUM SULFATE AMELIORATES CARBON MONOXIDE-INDUCED CEREBRAL INJURY IN MALE RATS

G. Bagheri[1], R. Rezaee [2], K. Tsarouhas[3], A.O. Docea[4], J. Shahraki[5], M. Shahriari[5], M.F. Wilks[6], H. Jahantigh[7], K. Tabrizian[8], A.A. Moghadam[8], S. Bagheri[9], D.A. Spandidos[10], A. Tsatsakis[11], M. Hashemzaei[5]

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[10]Laboratory of Clinical Virology, Faculty of Medicine, University of Crete, 71003 Heraklion, Greece

[11]Department of Forensic Sciences and Toxicology, Faculty of Medicine, University of Crete, 71003 Heraklion, Greece

P 15 ACCUMULATION OF CATIONIC FOLATE-ASSOCIATED LIPOSOMES IN CELL LINES WITH DIFFERENT FOLATE RECEPTORS EXPRESSIONS

A. Sapach[1,2], L.Kurbanova[2], A. Gileva[2], O.Selina[2], O. Koloskova[3], E. Markvicheva[2]

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[3] 2 NRC Institute of immunology FMBA, Moscow, Russia.

P 16 HYBRID CATIONIC POLYMERS COMPOSED OF ARGININE AND SPERMINE – SYNTHESIS AND PRELIMINARY IN VITRO CYTOTOXICITY STUDY

N. Zavradashvili[1], S. Kobauri[1], G. Otinashvili[1], L. J. del Valle[2], J. Puiggali[2], D. Tugushi[1], R. Katsarava[1]

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[2] Universitat Politècnica de Catalunya, c/Eduard Maristany 10-14, Barcelona E-08019, Spain

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P 17 **THE STUDY OF MOLECULAR MASS CHARACTERISTICS AND MICELLE FORMATION IN A SOLUTION OF AMPHIPHILIC OLIGOMERS USED TO INCAPSULATION OF DRUGS.**

E.V. Ivanovskaya, V.G. Kharitonova, T.S. Seregina, I.A. Derevnin, V.V. Mendrul, V.A. Dyatlov, A.L. Luss

D. Mendeleev University of Chemical Technology of Russia.

P 18 **MATRIX COPOLYMERIZATION OF ANILINE AND 2-AMINOPHENETHYL ALCOHOL USING A LACCASE-MEDIATOR SYSTEM**

M.E. Khlupova[1], O.V. Morozova[1], G.P.Shumakovich[1], I.S.Vasil'eva[1], E.V.Gromova[2], E.A.Zaitseva[3], A.I.Yaropolov[1]

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[2] Pirogov Russian National Research Medical University, Ostrovitianov str. 1, 117997, Moscow, Russia;
[3]Lomonosov Moscow State University, Faculty of Chemistry, Leninskie Gory 1/3, 119991, Moscow, Russia

P 19 **HUMIC ACIDS AND SILVER NANOPARTICLES AS ANTIMICROBIAL ADDITIVES**

A.F. Krivoshchepov[1], I.A. Butorova[1], T.V.Tikhonova[1], A.N. Kuskov[1,2]

[1]Department of Technology of Chemical Pharmaceutical and Cosmetic Products, Dmitry Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047 Moscow, Russia
[2]Department of Biomaterials, Dmitry Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047 Moscow, Russia

P 20 **DEVELOPMENT OF A METHODOLOGY FOR ANALYSIS OF LIQUID SOAP ANTIMICROBIAL ACTION**

M.S. Kuznetsova, I.A. Butorova, M.V. Sardushkin

Department of Technology of Chemical Pharmaceutical and Cosmetic Products, D.Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047 Moscow, Russia

P 21 **CATALYSIS OF AROMATIC AMINES OXIDATIVE POLYMERIZATION WITH METHYLENE BLUE**

Ya.O. Mezhuev, S.Yu. Levchishin, Yu.V. Korshak, A.L. Luss, V.A. Dyatlov, I.V. Plyushchii, M.I. Shtilman

D. Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation

P22 **SOLID PHASE SYNTHESIS OF CALCIUM STEARATE ON MODIFIED SCREW EQUIPMENT**

A.A. Momziakov, T.R. Deberdeev, R. Ya. Deberdeev

Kazan National Research Technological University, Kazan, Russia

P 23 **ANTI-ADHESIVE MATERIAL BASED ON HYDROPHOBIC CHITOSAN NANOPARTICLES**

K.S. Podkorytova [1], M.V. Konovalova [2], E.I. Kashirina [2], E.V. Svirschevskaya [2]

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[2] Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, GSP-7, Miklukho-Maklaya str., 16/10, 117997, Moscow, Russia

P 24 **HYDROGEL MATRIX CONTAINING POLYVINYLPYRROLIDONE, POLYELECTROLYTE AND CELLULOSE DERIVATIVES AS CARRIER FOR MEDICAL APPLICATIONS**

V.V. Smagina[1], T.V. Tikhonova[1], A.F. Krivoshchepov[1], A.N. Kuskov[1,2]

[1]Department of Technology of Chemical Pharmaceutical and Cosmetic Products, Dmitry Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047 Moscow, Russia
[2]Department of Biomaterials, Dmitry Mendeleev University of Chemical Technology of Russia, Miusskaya sq. 9, 125047 Moscow, Russia

P 25 **PH-SENSITIVE MULTI-LIPOSOMAL NANOCONTAINERS BASED ON CHITOSAN**

N.G. Smirnova[1], A.A. Efimova[2], D.A. Erzunov[2], N.V. Lukashev[2], G.G. Krivtsov[3], N.S. Melik-Nubarov[2], A.A. Yaroslavov[2]

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[2]M.V. Lomonosov Moscow State University, Faculty of Chemistry, Moscow, Russia
[3]I.I. Mechnikov Research Institute of Vaccines and Sera, Moscow, Russia

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O 01

BIOMATERIALS – MOVING FORWARD

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The area associated with the creation, research and use of biomaterials remains one of the most rapidly developing areas that unite the interests of various sciences and technologies - first of all, chemistry and technology of low-molecular and high-molecular compounds, medicine, biotechnology, agriculture, cosmetology, and ecology. This is confirmed by the volume of the market of biomaterials (more than $ 150 billion by 2020 with an increase over 5 years by 50%) and products using biomaterials (about $ 600 billion by 2020).

Over the past 10-15 years, the range of materials used in this field, both synthetic and natural, has expanded considerably. An example is ultra high molecular weight polyethylene, segmented polyurethanes, polyetheretherketone, microbial hydroxycarboxylic acid homo- and copolymers, and a number of others that have significantly suppressed widely used polymers, in particular, classical polyamides, high-pressure polyethylene, organosilicon poymers.

New approaches to the creation of products from polymeric biomaterials, such as electrospinning and 3D molding, the creation of various new nanoscale systems, which seemed to be exotic before, have been developed.

Firmly occupied their niches in the field of biomaterials inorganic (ceramic) and highly compatible carbon materials, products based on metal alloys.

At the same time, the problems of creating economically accessible polymeric materials with predetermined biodegradation periods for general-purpose products, materials for creating products with a consistently high level of hemocompatibility, materials for systems of targeted delivery of biologically active agents, in particular, for transfection, effective systems for bonding soft tissues (a number of other areas can be noted), although work in these areas is actively carried out in various countries, remained unsolved.

Thus, it can be stated that the field of biomaterials continues to have great prospects for development and one can expect in the near future the development of new types of biomaterials, in particular, compositional, as well as new methods of manufacturing products from biomaterials and the directions of their use.

O 02

ADVANCES IN ENGINEERING NANOSYSTEMS FOR DRUG DELIVERY

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Various pharmaceutical nanocarriers, including liposomes and polymeric micelles, are frequently used for the delivery of a broad variety of both soluble and poorly soluble pharmaceuticals to enhance the in vivo efficiency of many drugs. Now, within the frame of this concept, it is important to develop multifunctional stimuli-responsive nanocarriers, i.e. nanocarriers that, depending on the particular requirements, can circulate long; target the site of the disease via both non-specific and/or specific mechanisms, such as enhanced permeability and retention effect (EPR) and ligand-mediated recognition; respond local stimuli characteristic of the pathological site by, for example, releasing an entrapped drug or deleting a protective coating under the slightly acidic conditions inside tumors facilitating thus the contact between drug-loaded nanocarriers and cancer cells; and even provide an enhanced intracellular delivery of an entrapped drug with its subsequent delivery to specific intracellular organelles, such as nuclei, lysosomes or mitochondria. Additionally, these carriers can be supplied with contrast moieties to follow their real-time biodistribution and target accumulation. Among new developments to be considered in the area of multifunctional pharmaceutical nanocarriers are: novel liposomal nanopreparations for targeting both, bulk and stem cancer cells; drug- or/and RNA-loaded delivery systems additionally decorated with cell-penetrating peptides for the enhanced intracellular delivery; "smart" multifunctional drug delivery systems, which can reveal/expose temporarily hidden functions under the action of certain local stimuli characteristic for the pathological zone (such as lowered pH, pedox-conditions, hypoxia, or locally increased expression of certain enzymes); new means for controlled delivery and release of siRNA; approaches for intracellular drug delivery and organelle targeting; application of nanocarriers co-loaded with siRNA and drugs to treat multidrug resistant tumors; theranostic nanopreparations; and nanopreparations based on novel derivatives of dendrimers.

O 03

COMPARATIVE PHYSIOLOGY OF VISION: THE MECHNAISMS OF ADAPTATION OF INVERTEBRATE AND VERTEBRATE EYES TO LIGHT HABITAT; THE PROBLEM OF "LIGHT POLLUTION" FOR HUMANS

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In the course of evolution and natural selection, the vision of invertebrates and vertebrates is well adapted to the changing conditions of the light environment. The mechanisms of such adaptation are the subject of comparative physiological research. Unfortunately, violations of these natural mechanisms by the human community, the so-called "light pollution", lead to the adverse effects on human vision and health.

Invertebrate vision

Together with our Finnish colleagues, we carried out a detailed study of adaptation of vision of two populations of the same species of shrimp Mysis relicta - sea and lake that were divided about ten thousand years ago. We have investigated the mechanisms of visual adaptation to different light environment and the mechanisms of the steadiness of the eye structures to the hazard of light damage.

Vertebrate vision

There are many well-known examples of the effective adaptation of the vision of vertebrates to the different light habitat. One such example is the different spectral sensitivity of the eye and, accordingly, different absorption spectra of visual pigments in fish living at depths or close to the water surface. One of the ways to protect the retina of many species of fishes from the hazard to the short-wave light damage is a yellow-colored cornea, like sunglasses. In terrestrial vertebrates, the cut-off filter in the system of optical protection is the lens. In many animals that live in a bright light environment, such as squirrels, the lens is intensely yellow from birth.

Human vision

In humans, the lens is colorless, but with age it turns yellow. Due to this yellowing, an additional yellow filter is «introduced» in front of the retina, which gradually cuts off the violet-blue part of the spectrum and protects against the ever-increasing danger of light damage. Creating an artificial lens of the eye (colored intraocular lens), we have imitated the spectral characteristics of the human's eye natural lens with age.

Modern white LEDs have a pronounced emission band in the blue region of the spectrum of 440–460 nm, which completely covers the spectrum of the photochemical damage to the retina and the pigment epithelium. Such radiation is an increased danger to the eyes of children and adolescents, since their lenses are twice as transparent in this region of the spectrum than the lenses of adults. Therefore, the use of LED lighting, primarily white LEDs, in children's institutions, in our opinion, can have completely unpredictable negative consequences (known in physiology of vision as a "blue light hazard").

Human society has increased its exposure to artificial illumination. Light acts on the retina to fulfill two important roles: (1) the visual function and (2) non- visual functions, such as the synchronization of circadian rhythms, pineal melatonin suppression and pupil light reflexes. The excess of illumination may cause or accelerate retinal diseases. It is a fact that civilization makes the night brighter. Disruption of the environmental light-dark cycle can cause abnormal circadian rhythm and may result in various psychological or physiological human dysfunctions. Light environmental alteration called 'light pollution' spreads widely across the world. The study of light pollution and ocular health is now beginning to receive global attention.

O 04

NEUROENZYMOLOGY – NEW CHALLENGES AND NEW SOLUTION

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Research on the molecular basis of sensory perception, recording systems, information storage, decision making and neuro-physiological responses is one of the most relevant areas of modern science.

Fundamentally difficult is the set of tasks for studying chemical processes directly in human neural networks. The most promising is the approach developed by us, based on functional magnetic resonance imaging and spectroscopy, which allows identifying the excitation zones and investigating chemical processes directly in the human brain in real time (Dr. Sc. N. A. Semenova, D. Sc. T. A. Akhadov with coauthors).

We have experimentally investigated the dynamic responses of the neural network to external signals, the reactions of the system when solving specific problems with the kinetic analysis of BOLD signals and, consequently, the dynamic behavior of a number of key metabolites. The kinetics of the conversion of N-acetylasparginic acid was investigated, a detailed chemical-kinetical modeling of the process was carried out, the trigger effect and autostatization of the metabolite were described. The autostatization effect and the "on-off" trigger of the system are related to the nonlinear nature of the dependence of the enzyme reaction rate on the substrate concentration.

A kinetic model based on experimental data includes the effect of the described vasodilatory effect, initiated by a nerve impulse, kinetic responses at the level of N-acetylasparaginic acid, aspartate, glutaminate, acetate and N-acetylcholine.

The mechanisms of action of key enzymes of the system (N-acetylaspartase and cholinesterase) are described on the basis of first principles with the use of QM / MM approximations.

On the basis of the developed concepts, the possible molecular kinetic causes of a number of pathologies (Canovane's disease, schizophrenia, myostenia), as well as individual sensitivity to drugs, are analyzed.

O 05

BIOASSAY ON THE BASE OF FUNCTIONALYZED NANOPARTICLES

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The use of nanoparticles as carriers for receptors or detectable markers is an intensively developing direction of modern analytical chemistry. These compounds allow (i) combining possibilities of homogeneous and heterogeneous analytical interactions, (ii) integrating specific analyte-receptor complexes with markers that can be detected in extremely low concentrations, (iii) realizing multiparametric assays and multistage amplification of analytical signals. The report presents the development of bioassays with nanoparticles that were functionalized by bioreceptors and the results of their use to detect compounds of different classes.

Based on experimental data and studies of mathematical models, the relationship between the optical characteristics of the nanoparticles, the affinity of bioreceptor-ligand interactions and the theoretically possible limits of detection for analytical systems with their use is determined. A set of parameters is proposed for comparative evaluation of nanoparticles as bioanalytical markers. The advantages of fluorescent markers in comparison with colorimetric ones are characterized. The possibilities of magnetic nanoparticles as markers and carriers for the separation of reagents are considered.

The influence of the composition and reactivity of the nanoparticle–bioreceptor conjugate on the characteristics of the assay with its use is described. Methods for assessing the conjugates' properties are proposed. The conjugates obtained by adsorption, covalent and bioaffine immobilization are compared. Various schemes for amplification of analytical signals are considered including the aggregation of functionalized nanoparticles in the course of the assays.

The capabilities of aptamers, oligonucleotide receptors, have been characterized to evaluate them as an alternative to antibodies in bioanalytical systems. Sensitive detection of low molecular weight analyte (mycotoxin) using aptamers and registration of fluorescence anisotropy has been shown. The given assay format allows testing without prolonged incubations and separations, detecting specific complexes directly at the moment of their formation.

The assay formats for simultaneous determination of several compounds using a combination of different nanomarkers and/or the formation of separated binding zones with different specificities are considered.

The validation of the proposed new formats of immunoenzyme assay, immunochromatography and polarization fluorescent assay included their use for detection of haptens (antibiotics, mycotoxins, heavy metals), proteins (cardiac markers) and viral/bacterial pathogens in different biomatrixes (milk, grains, plants, blood etc.). The obtained results confirm the efficiency of functionalized nanoparticles and their complexes as tools decreasing the limit of detection by one-two order of amplitude with stored rapidity (10-20 minutes) and simplicity of the assays.

The work was supported by the Russian Foundation for Basic Research (grant 18-08-01397).

O 06

INFLUENCE OF ARYLOXYALKANOIC ACIDS DERIVATIVES ON SOIL MICROBIOCENOSIS

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Introduction. Study of the vitality of soil microbial populations under the influence of the broad-spectrum action herbicide derivative of aryloxyalkanoic acids.

Materials and methods. Substance (a.s.) (IUPAC name – (4-chloro-2-methylphenoxy)acetic acid) according to hygienic classification of pesticides by degree of danger is a highly hazardous compound by carcinogenic effect (hazard class 2C in Russian Federation), according to the classification of the IARC - 2B. Substance in form of aqueous solution was introduced into sandy soil with weight of 5 kg in concentrations:

0,52 mg/kg (maximum recommended application rate in agriculture); 5,2 mg/kg 10 times lower of the maximum rate. The experiments carried out three times in stable temperature (+25C) and humidity (60%). Bacterial suspension by density of 10 ME/ml (3 units McFarland Standard) put on 1 kg of soil. Isolation of microorganisms from soil samples of experimental and control models carried out by standard methods in bacteriology, identification using an analyzer (Vitec-2-compact bio Merieux) on 1, 3, 5, 7, 10, 14, 30, 45, 60 days of experiment. The dynamics of the soil microbiocenosis state was evaluated by the survival of saprophytic microflora (total microbial number, CFU/g) and sanitary-indicative facultative anaerobic microorganisms (coliform bacteria and E. coli, CFU/g)

Results. Established multidirectional action of active substance on the microbiocenosis of soil. There was a tendency of saprophytic microflora multiplication in the soil irrespective of the concentration of the substance. Indicators of total microbial numbers did not exceed 50% of the control level ($t \geq 1.2$). The influence of the substance on the vitality of saprophytic soil microflora was stopped by the 30th day of the experiment. Under the influence of the studied concentrations of the substance there was a tendency to growth inhibition of coliform bacteria and E. coli in the soil during the first three days of the experiment. Quantity reduction in the number of coliform bacteria and E. coli in the soil reached 11.3-34.7% in compared with the control. By the 10 day of the experiment there was no differences discovered in the level of coliform bacteria and E. coli in the experimental samples and control

Conclusions. The substance can be estimated as weakly acting on the microbiocenosis of the soil.

O 07

GEEN "BIOPLASTICS" IN SOLVING THE GLOBAL PROBLEM OF A POLYETHYLENE DUMP

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Increasing environmental awareness and problems caused by accumulation of synthetic plastics, whose annual production has reached 350 million tons, in the biosphere have attracted special attention to studies related to biotechnological processes of producing degradable polymers and their practical implementation Plastic waste ruins municipal sewage and drainage systems and pollutes water environments. Greenpeace reports that up to 10% of the plastic produced every year gets into the Global Ocean. Among the promising «green» plastics are polyhydroxyalkanoates (PHAs. These polymers are promising materials for fabricating biomedical devices, degradable packaging for food and drinks, personal hygiene products, and devices and formulations for municipal engineering and agriculture.

Researchers of the Institute of Biophysics SB RAS and Siberian Federal University tested different modes of cultivation of hydrogen-oxidizing bacteria on the gaseous substrate, such as autotrophic synthesis of protein or poly(3-hydroxybutyrate) and PHA copolymers using electrolytic hydrogen; and синтез-газ; sugars, organic and fatty acids, vegetable oil. Physicochemical properties and mechanical properties of PHA having different chemical composition were studied. The laws governing the destruction of polymers in soil and aquatic natural ecosystems are investigated. Polymer products of various types for various applications were obtained, - for medicine and technical purposes, as destructible packaging and containers. A new line of research in bioplastics has been formulated and deployed to create eco-friendly agropreparations of a new generation. A family of agricultural preparations forms using biodegradable PHAs as a basis was constructed and characterized. In soil ecosystems with model weed plants, as well as in crops of cultivated plants infected with pathogens of root rot or weeds, the effectiveness of pre-emergence application of the developed long-term forms of pesticides deposited in PHA was shown. It opens prospects for the creation of long-term and targeted newgeneration pesticides to reduce application rates and the uncontrolled spread of xenobiotics in the biosphere.

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O 08

TRANSIENT INCOMPLETE SEPARATION FACILITATES FINDING ACCURATE EQUILIBRIUM DISSOCIATION CONSTANT, KD, OF PROTEIN–SMALL MOLECULE COMPLEX

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Current practical methods for finding the equilibrium dissociation constant, Kd, of protein–small molecule complexes are mainly biosensoric and calorimetric. They have inherent sources of inaccuracy; immobilization of molecules on sensors and heat of side reactions often lead to errors in Kd as large as 2–3 orders of magnitude [1]. We have recently introduced "Accurate Constant via Transient Incomplete Separation" (ACTIS), a non-biosensoric and non-calorimetric approach for finding Kd, which appears to be free of inherent sources of inaccuracy [2]. Conceptually, in ACTIS, a short plug of the pre-equilibrated protein–small molecule mixture is pressure-propagated in a capillary, causing fast transient incomplete separation of the complex from the unbound small molecule. A superposition of signals from these two components is measured near the capillary exit and used to calculate a fraction of unbound small molecule, which, in turn, is used to calculate Kd. In the proof-of-principle work, we confirmed ACTIS validity theoretically, verified its accuracy by computer simulation, and demonstrated its practical use for measuring Kd of protein–drug binding with mass-spectrometry as a detection mode. Owing its suggested accuracy, ACTIS has a potential to become a reference-standard method for finding Kd of protein–small molecule complexes.

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O 09

ANTIMICROBIAL PROFILING OF DIFFERENTLY SURFACE-FUNCTIONALIZED SELENIUM NANOPARTICLES

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Selenium (Se), a nonmetal, has been called 'essential toxin' as it is necessary trace element for a variety of organisms but toxic at elevated concentrations. Indeed, selenocysteine is called the 21st amino acid as it is a constitutive component for different enzymes e.g., in mammals, but also in bacteria. Se is considered beneficial for humans and Se food supplements are available in the drug stores.

As dose makes the poison, the toxic action of Se at elevated concentrations could be harnessed for creation of novel antimicrobial compounds e.g., to combat the increasing resistance of bacteria to conventional antibiotics. The most efficient antimicrobial metals are silver, copper and zinc that are toxic at <1 mg/L and applicable as nanoparticles (NPs). Modification of size and surface of NPs, in turn, allows tuning of cell-NP interactions crucial for antimicrobial outcome.

We evaluated the antimicrobial potency of Se0-NPs (primary size ~80 nm) and selenite (Na2SeO3). Differently functionalized Se0-NPs were synthesised by reduction of Na2SeO3 with ascorbic acid in the presence of polyvinylpyrrolidone, bis(2-ethylhexyl)sulfosuccinate, polyacrylic acid and poly-L-lysine, yielding positively charged (PLL) and negatively charged (the rest of the coatings) Se0-NPs of low aqueous solubility, <4%.

Gram(+) Staphylococcus aureus, Gram(-) Escherichia coli, naturally luminescent Vibrio fischeri and yeast Saccharomyces cerevisiae were used for testing. The Se-compounds were evaluated for toxicity in the Spot test (all microbes) and using the 30min V. fischeri bioluminescence inhibition test (a Flash Assay). For the Spot test V. fischeri was incubated for 4h and 24h with Se-compounds in 2% NaCl and the rest of the microbes in distilled water and evaluated for post-exposure growth on nutrient agar for determination of minimal bactericidal concentrations (MBC).

The studied Se-compounds were most harmful to marine bacteria V. fischeri, down to 24h MBC of Se0-NPs ~13 mg Se/L. For E. coli and S. cerevisiae the studied Se-compounds were not toxic (4h and 24h MBC>100 mg Se/L). The same was true for S. aureus after 4h exposure but not after 24h exposure where Se0-NPs were slightly more toxic (MBC 50-100 mg Se/L) than selenite (MBC >100 mg Se/L). Se0-NPs were more toxic than selenite also in the V. fischeri Flash Assay (30min EC50 ~30 and >100 mg Se/L, respectively).

This study provides new information on effects of Se0-NPs to various types of microbes important for hazard evaluation of this 'essential toxin'.
This work was supported by Estonian grant IUT 23-5 and Croatian grant HRZZ-IP-2016-06-2436.

O 10

SYNTHETIC OLIGOSACCHARIDES AND GLYCOCONJUGATES AS INDISPENSABLE TOOLS FOR THE DEVELOPMENT OF IEA DIAGNOSTIC KITS FOR THE DETECTION OF PG-AMOUNTS OF MICROBIAL POLYSACCHARIDES

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Antigenic polysaccharides of microbial pathogens can be served as markers for the development of diagnostic kits for immune-enzyme assays (IEA) of different types. Unfortunately, in many cases parent natural polysaccharides of bacteria, fungi and other types of pathogens have very limited availability in the individual state, can be difficult for biotechnological cultivation and may have too complex structures associated with irregularity or masked irregularity. Due to these limitations the chemical synthesis of oligosaccharides representing immune determinant fragments of microbial polysaccharides opens the way towards efficient synthetic haptens, immunogens, coating antigens and other glycotechnological instruments required for preparation, selecting and assessing carbohydrate specificity and affinity of monoclonal antibodies as well as for assembling sandwich IEA under different technological platforms that will be discussed in the lecture.

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O 11

TOWARDS THE BIOFABRICATION OF HUMAN THYROID GLAND CONSTRUCTS: 3D CULTIVATION OF THYROCYTES, THYROID FOLLICLES, AND MICROORGANS

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Introduction: The implantation of functional thyroid tissue-engineering constructs (TIC) could be considered as a promise alternative to traditional hormone replacement therapy in patients after thyroidectomy. Therefore the development of methods for scalable and reproducible cultivation of tissue fragments obtained from thyroid gland (TG) is a necessary stage in the implementation of this approach. The aim of study was the development of methods for prolonged cultivation of thyrocytes (TCs), thyroid follicles (TFs), and microorgans (MO) isolated from human TG tissue.

Methods: The study was performed on normal tissue samples obtained after thyroidectomy in cancer patients (n = 31). TCs, TFs and MOs were isolated by mechanical disaggregation and then maintained in semipermeable plate inserts up to 4.5 months on the bioactive hydrogel composed of human platelet lysate. The viability of cells was estimated by DiI and MTT staining. The proliferation was studied by staining for Ki-67, while the hormone-producing ability by NIS and thyroglobulin expression. The presence of progenitor cells was revealed using stem cell marker Oct 3/4. The morphometry of TFs was performed at different stages of experiments.

Results: During the 3D cultivation of single TCs, the early (within 7 days) selection of a minor (< 5% of total) population of Oct3/4+ cells was observed. These cells formed local "nests" and then new TFs, in the wall of which the small amount of Ki-67+ cells with normal epithelial polarity and the ability to produce TG could be detected.

At the same time, the 3D cultivation of TFs up to 2 months resulted in some increase in their size (by 13.9 ± 1.29%). Simultaneously TFs slowly converged, thus forming conglomerates. Single Ki-67+ could be also detected in follicle walls. At the same time, TCs in TFs retained the ability to produce TG after 4.5 months in culture.

The 3D cultivation of thyroid MOs for 21 days demonstrated the stability of their follicular structures with clear visualization of NIS+, TG+, and single Ki-67+ cells. The accumulation of collagen-rich connective tissue in culture gradually enveloped MOs that resulted in tissue mono fragment formation. Single fibroblast-like proliferating Ki67+ cells were visualized at the periphery of collagenous structures.

Conclusions: As a result, we developed a novel system for 3D cultivation of human thyroid tissue fragments with different levels of complexity and maturity (TCs, TFs, MOs), that can be used for the biofabrication of thyroid TICs intended for fundamental and clinical applications.

O 12

NEW BIODEGRADABLE FIBRILAR COMPOSITES ON THE BASE OF POLY(3-HYDROXYBUTYRATE) AND POLYLACTIDE FOR SELECTIVE PURIFICATION OF SEWAGES FROM OIL

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The problem of creation of the biodegradable composite materials decomposing under the environmental action on compounds harmless for nature, which can be used for sorption of the oil products and purification of sewages, is very urgent at present. The nanofibrillar composites on the base of the biodegradable polylactide (PLA) and poly(3-hydroxybutyrate) (PHB) represent a new generation of such highly-productive selective absorbents for oil under technogenic catastrophes.

The highly-porous ultrathin nanofibres and nanowoven materials of different composition on a basis of these polyesters were obtained by the electrospinning method. For production of homogeneous mixtures the preliminary solid-phase blending of polyesters under conditions of shear deformation was made. The high sorption efficiency of these composites relative to oil as compared with the currently used sorbents was demonstrated. Moreover, the advantage of the proposed systems is their biodegradability supposing their further utilization, and the revealed moderate water sorption make these composites promising materials as eco-friendly sorbents for oil products.

The work was supported by Russian Foundation for Basic Research (grant 18-29-05017-mk).

O 13

CHITOSAN-BASED BIOSORBENTS: MODIFICATION AND APPLICATION FOR SORPTION OF HEAVY METALS, DYES AND RADIONUCLIDES

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Chitosan derivatives are widely used for purification of drinking water and medical use from dyes and organic highly toxic compounds, heavy metal ions, radionuclides and other harmful substances [1,2]. Among the main directions of the use of sorbents based on chitosan, it is possible to distinguish the purification of drinking water and medical use from dyes and organic highly toxic compounds, heavy metal ions, radionuclides and other harmful substances [1-3]. However, the solubility of chitosan in aqueous solutions at low pH and, conversely, the low water permeability of chitosan-based materials at pH≥6 limit the use of unmodified chitosan in the adsorption of metal ions and dyes [3].

One of the ways to overcome the shortcomings of chitosan as an adsorbent is the crosslinking of chitosan to prevent its dissolution in acidic media. Carrying out the process of chitosan gelation in cryogenic conditions allows to obtain supermacroporous cryogels with communicating pores, which structure provides high kinetic and dynamic characteristics of the sorption process, insoluble in water in the entire pH range, in the presence of glutaraldehyde [4]. Modification of chitosan cryogels by pyridoxal 5'-phosphate led to a sharp increase in sorption capacity in relation to radionuclides and copper ions. A method of producing chitosan-containing cryogel in the absence of a crosslinking reagent by crioglobuline joint solution of the hydrochloride of chitosan and polyvinyl alcohol with the subsequent transfer of chitosan into the form of the base by deproteinizirovanny amino groups in pairs of ammonia [5]. The sorbent obtained under such conditions contains small particles of the discrete phase of chitosan (2-5 μm in size) uniformly distributed in the volume of the porous matrix of the composite cryogel of polyvinyl alcohol. This structure of the sorbent ensured the availability of chitosan amino groups during the sorption of dyes from their aqueous solutions. The sorption capacity of the obtained cryogels in relation to acid dyes is 10 times higher than the dye content on wool fibers under their dyeing under optimal conditions.

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O 14

MECHANISMS OF CROSS-LINKING OF CHITOSAN WITH ALDEHYDE DERIVATIVES

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Hydrogels based on chitosan are widely used in various fields: medicine, pharmaceutics, tissue engineering, chromatography, environmental protection, etc. Hydrogels represent three-dimensional polymer networks that absorb and hold up 10000 % of water or biological fluids in relation to their dry weight. In order to obtain stable hydrogels crosslinking reagents should be added to polymer solution. The most common crosslinking reagent for chitosan today is glutaraldehyde (GA). During its interaction with chitosan not only cross-linking of the polysaccharide chains occurs, but also aldol condensation of GA, leading to the formation of products of irregular structure.

The number of publications devoted to the development and use of materials on the basis of chitosan obtained using dialdehydes and alternative covalent crosslinking reagent of natural origin genipin (GP) is steadily growing. The use of cross-linking reagents provides stable, water non soluble three-dimensional matrix for tissue engineering, sorbents, hydrogel metal catalysts, carriers for biologically active compounds, proteins, cells, and other materials.

Hydrogels modified of chitosan modified with GP are less toxic but contain by-products and are blue colored. The change of cross-linking degrees by varying the process conditions (concentration of crosslinking reagent, pH and temperature of the reaction) allows adjusting and optimizing the properties of the obtained materials. This paper summarizes authors own data to study the mechanisms of chitosan cross-linking.

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O 15

LIBRARY OF CATIONIC POLYMERS COMPOSED OF POLYAMINES AND ARGININE AS GENE TRANSFECTION AGENTS

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Combinatorially synthesized materials, especially cationic polymers (CPs), with gene transfection function hold great promise in nanotechnology. However, the main limitations of the existing CPs (such as polyethylenimine (PEI), poly-L-arginine (Poly-Arg), or polyamidoamine-based dendrimers, etc.) as gene transfection agents are high cytotoxicity in the physiological environment. We have developed novel CPs composed of polyamines - endogeneous tetraamine spermine (Spm) and synthetically made triamine N-(2-aminoethyl)-1,3-propanediamine (Apd) for incorporating sec-amino groups and imparting PEI-like structure to the CPs backbones. Naturally occurring building blocks such as amino acid arginine (R) was also used for incorporating guanidine-groups into the CPs. The cytotoxicity of resulting CPs - polyureas (PUs), polyamides (PAs) such as polysuccinamides (PSuAs) and R-attached polymalamides (RPAs) was evaluated using murine and human fibroblasts and carcinoma cell lines. The cell compatibility screening revealed that the CPs made of Apd are less cytotoxic compared to Spm-based analogues. From the novel polymer library, total of six polymers were further studied for oligonucleotide (pDNA) complexation and transfection abilities. Highly water-soluble CPs formed nano-sized polyplexes with pDNA at rather low CP/pDNA weight ratios, showed less cytotoxicity and higher transfection ability compared to widely-used PEI as well as commercially available transfection agents. Furthermore, new CPs showed selective transfection activity towards certain cell lines (4T1, HeLa, NIH 3T3 and CCD 27SK), which is important for their potential applications in gene therapy [1].

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O 16

TOXICITY OF DIFFERENTLY SIZED AND SURFACE-FUNCTIONALIZED SILVER NANOPARTICLES TO YEAST SACCHAROMYCES CEREVISIAE

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Infections caused by microorganisms are often difficult to treat because microbes can rapidly adapt to conventional antibiotics. Therefore, there is a growing need for efficient antimicrobials to suppress the growth of pathogens. One of the promising types of such antimicrobials is based on Ag nanoparticles (AgNPs). Although the release of Ag ions, destabilization of cell membrane, interactions with thiol groups, inactivation of enzymes, and generation of reactive oxygen species (ROS) are thought to play the key role in AgNPs antimicrobial mode of action, the full understanding how the different physical-chemical properties can modulate AgNPs biocidal potency is still under investigation. Moreover, majority of information on AgNPs toxicity mechanisms concerns bacteria and relatively little is known on toxic effects of NPs to an important group of unicellular eukaryotic microorganisms – yeasts and fungi.

In this study the modulatory effect of size and surface functionalization on toxicity of AgNPs to yeast Saccharomyces cerevisiae BY4741 was assessed. S. cerevisiae was used as a fungal model. 10 and 80 nm citrate-coated (negatively charged) and branched polyethylenimine (bPEI) coated (positively charged) AgNPs and AgNO3 as ionic control were studied.

Yeast cells were exposed to the different concentrations of studied compounds in deionized water for 24 h at 30°C and evaluated for the viability by post-exposure colony-forming ability on agar medium. Particle-cell interactions (adsorption onto the surface of cell and internalization) were assessed by SEM, TEM and confocal laser scanning microscopy (CLSM) in the reflection mode.

We showed that AgNPs toxicity to yeast was size- and charge dependent: 24-h IC50 values ranged from 0.04 (10nAg-bPEI) up to 8.3 mg Ag/L (80nAg-Cit). 10 nm AgNPs were 5–27 times more toxic than 80 nm AgNPs and bPEI-AgNPs 8–44 times more toxic than citrate-AgNPs. SEM and TEM visualization showed that bPEI-AgNPs but not citrate-AgNPs adsorbed onto the yeast cell's surface. However, according to CLSM all the studied AgNPs, whatever the size and coating, ended up within the yeast cell. Toxicity of citrate-AgNPs was largely explained by the dissolved Ag-ions but the bPEI-AgNPs showed mainly particle-driven effects. Therefore, size, and especially surface-functionalization/charge of AgNPs can be efficiently used for the design of new more efficient antifungals.

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O 17

ANTIBACTERIAL METAL-BASED NANOPARTICLES: TOXICITY, MECHANISMS AND SAFETY TO HUMAN CELLS

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Our work during the last decade has been focused on the toxicity of metal-based nanoparticles (NPs) to a range of organisms/cells including bacteria and mammalian cells in vitro. From all studied NPs, Ag, ZnO and CuO NPs were the most efficient antibacterials being effective in the range of 0.03–100 mg/L [1]. By combining antibacterial tests with mechanistic studies and comparative data on antibacterial activity of respective metal salts, we revealed the mechanisms of bacterial toxicity of metal-based NPs: the antibacterial efficiency of NPs depended mostly on dissolution of NPs, their size, surface functionalization and cell-NP contact. For example, we showed that 10 nm Ag NPs were better antibacterials compared to 50 nm NPs, cell-NP contact increased antibacterial efficiency of Ag NPs and that bacterial plasma membrane was the main cellular target of Ag NPs in Pseudomonas aeruginosa and Escherichia coli [2-4]. In addition, we showed that the toxic effects of metal-based NPs can be significantly tuned with the surface functionalization, and the effect of the surface functionalizations is different for bacteria and human cells. For example, we showed that CuO NPs functionalized with polyethylene glycol or carboxyl group are efficient antibacterials but they are less toxic to human cells (HACAT keratinocytes and THP-1 derived macrophages in vitro) compared to unfunctionalized CuO.

Thus, by combining the knowledge on mechanisms of toxicity of NPs and by manipulating the size and surface functionalization of NPs, we are able to fine-tune the NP-cell interaction and design NPs with desired antibacterial properties and low toxicity to human cells.

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O 18

ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) WITH PHOTOMETRIC AND CHEMILUMINESCENT DETECTION OF FUNGI

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The immunochemical methods based on the specific and high affinity antibodies are widely used for high-throughput screening (HTS) and monitoring of food contaminants. At first it is important for detection of poisons and toxic organic chemicals like pesticides, antibiotics, mycotoxins and others.

The Enzyme-Linked Immunosorbent Assay (ELISA) is one of widely used immunoassays. The ELISA could be optimized with photometric and chemiluminescent detection. Moreover, ELISAs are modified to make its more simple, quick and cheap without any instruments or with using available device like smartphone.

The specific antibodies for pathogens of agricultural plants (fungi): Fusarium spp., Alternaria spp., Aspergillus fumigatus, Claviceps spp. (ergot) were produced and different ELISAs for express immunodetection of fungi were developed. The experimental ELISA kits for fungi were produced by "XEMA" (Russia) and were used as simple, quick, preliminary test for detection fungi in cereals (wheat, rye, barley).

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O 19

CHITOSAN-BASED SCAFFOLDS FOR TISSUE ENGINEERING : PREPARATON AND IN VITRO EVALUATION

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Natural polysaccharide chitosan (Chit) is of great interest for tissue engineering and regenerative medicine, since Chit-based matrices (scaffolds) are biocompatible and biodegradable. More over, the scaffolds have antibacterial and bioadhesive properties. They can be easily modified due to chitosan amino groups, in order to develop composite matrices with desirable physicochemical properties for cell growth, proliferation or differentiation.

The objectives of the study were as follows: 1) to prepare Chit-based matrices, namely films (2D) and macroporous hydrogels (3D); 2) to study their structure and physicochemical properties; 3) to evaluate in vitro cell growth and proliferation or differentiation.

In this study, two types of Chit-based scaffolds were used: 1) matrices from copolymers of Chit with oligo (L, L- /L, D-lactides); 2) composite Chit-hyaluronic acid (Chit-HA) and Chit-HA-fibroin matrices.

To obtain copolymers by solid-phase synthesis, Chit (MM 60 kDa, DD 0.9) and oligo (L, L- /L, D-lactides), MM 5 kDa, were used. Composite Chit-HA hydroges were fabricated from Chit (MM 320 kDa, DD 0.9), HA (MM 5 and 30 kDa), silk protein fibroin. To increase mechanical stability of the Chit-HA matrices, Chit macromolecules were cross-linked with natural herbal compound genipin, followed by the formation of a Chit-HA polyelectrolyte complex, and the obtained matrices were lyophilized.To enhance biocompatibility, fibroin was added to Chit-HA matrices. The films were casted from 2 wt.% acetic acid solution and .also dried by lyophilization.The structure of the hydrogels was studied using confocal laser microscopy, and the cytotoxicity of the extracts obtained from them was investigated using the MTT-test. All hydrogels were shown to support the growth and proliferation of mouse fibroblasts (L929) and human mesenchymal stromal cells (MSC) when cultured for 7 days in vitro (MTT test). Osteodifferentiation of MSC was assessed by testing the activity of alkaline phosphatase.

Thus, Chit-based scaffolds are promising biomaterials for tissue engineering and regenerative medicine.

O 20

LYSOSOMAL DELIVERY OF THE ENZYME, TTP1, LOADED IN EXTRACELLULAR VESICLES AND ITS ENHANCED DISTRIBUTION TO THE BRAIN IN THE ANIMAL MODEL OF BATTEN DISEASE

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Extracellular vesicles (EVs) (exosomes and microvesicles) are promising natural nanocarriers for delivery of various types of therapeutics. We reported earlier exosome-based formulations for neurodegenerative diseases and cancer. In the work presented the use of macrophage-derived EVs for brain delivery of a soluble lysosomal enzyme tripeptidyl peptidase-1, TPP1, to treat a lysosomal storage disorder, Neuronal Ceroid Lipofuscinoses 2 (CLN2) or Batten disease was shown. TPP1 was loaded into exosomes using two methods: (i) transfection of parental exosome-producing macrophages with TPP1-encoding plasmid DNA (pDNA), or (ii) incorporation of therapeutic protein TPP1 into naive empty exosomes. For the former approach, EVs released by pre-transfected macrophages contained the active enzyme, and TPP1-encoding pDNA. To achieve high loading efficiency by the latter approach, sonication, or permeabilization of exosomal membranes with saponin were utilized. Both methods provided proficient incorporation of functional TPP1 into exosomes (exoTPP1). It should be noted that EVs significantly increased stability of TPP1 against protease degradation, and provided efficient TPP1 delivery to target cells in in vitro model of CLN2. The majority of exoTPP1 (~ 70%) was delivered to target organelles, lysosomes. Finally, a robust brain accumulation of exosomal carriers and increased lifespan was recorded in late-infantile neuronal ceroid lipofuscinosis (LINCL) mouse model following intraperitoneal administration of exoTPP1. Overall, exosome-based formulations have a potential to be a versatile strategy to treat different lysosomal storage disorders.

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O 21

MODERN TREATMENT APPROACHES OF POST-BURN SCARS

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Key words: nanodispersed cerium dioxide (NCD), cerium chloride (III), burn injury, anti-inflammatory effect, scar tissue.

Recent advances in nanobiotechnology have led to nanodispersed cerium dioxide (NDC) investigation, which has antioxidant properties. Treatment of rat neuron culture with NDC provides an increase in life expectancy and decrease of cell damage as a result of oxidative stress caused by hydrogen peroxide action or ultraviolet radiation in vitro [1]. Potential biological applications of NDC have also been noted in studies on primary cells protection from radiation therapy harmful effects [2], in prevention of retinal degeneration caused by intracellular peroxides [3], and spinal cord neurons protection from oxidative damage and a number of neurodegenerative diseases [4].

NDC can participate in intracellular redox processes due to its ability in oxidation degree changing. The NDC redox properties depend on particle size and hydrogen index (pH) level of the medium. For example, antioxidant activity reveals by having the smallest size at neutral or alkaline hydrogen index level of the medium [5], and pro-oxidant properties are manifested when hydrogen index is lower 7 [1].

The biological activity of water-soluble cerium salts reveals in stimulation human fibroblasts proliferation, limiting local sepsis, inflammation and systemic immunosuppression. Cerium ions inhibit histamine release in human granulocytes by blocking of calcium-dependent ATPase, and effectively inhibit this enzyme in epidermal Langerhans cells, which play an important role in atopic eczema and immune response in the skin [6, 7].

Nowadays despite of careful attention to cerium, information about the effects in living systems remains fragmented. There are only few papers on dosage and side effects of cerium-based drugs. Cerium toxicity data are very contradictory and require further investigation [8].

Our results of the in vivo research indicate that cerium compounds, both in the nanodisperse and water-soluble forms, have a tissue-preserving and anti-inflammatory effects, provide formation of more complete regenerate compared to the control, while the regeneration ability of tissues adjacent to the primary burn injury is being improved.

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O 22

BAYESIAN NETWORKS APPLICATION FOR THE PREDICTION OF CELLULAR EFFECTS FROM GENOME-WIDE TRANSCRIPTOMICS STUDIES OF EXPOSURE TO NANOPARTICLES.

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This study bridges physicochemical properties of Nanoparticles (NPs), exposure conditions and in vitro characteristics with biological effects of NPs on a cellular level. The data are derived from transcriptomics studies and the bridging is achieved by implementing Bayesian Networks (BNs) classifier developed ad hoc. The BN structures are derived either automatically or methodologically and the data are classified either raw or pre-processed. The pre-processed data-driven BN has better performance compared to automatically structured BN and the raw data-driven BN. The pre-structured BN captures inter relationships between NPs properties, exposure conditions and in vitro characteristics and links those with cellular effects based on statistic correlation findings on the dataset. Dose, NP and cell line variables are the most influential attributes. The BN methodology proposed in this study successfully predicts a number of cellular disrupted biological processes such as cell cycle and proliferation, cell adhesion and extracellular matrix, DNA damage and repair mechanisms etc., with a success rate >80%. The model validation from independent data shows a robust and promising methodology for incorporating transcriptomics outcomes in a hazard and, extendedly, risk assessment modelling framework by predicting affected cellular functions from experimental conditions.

O 23

MACHINE LEARNING PREDICTION OF NANOPARTICLE IN VITRO TOXICITY: A COMPARATIVE STUDY OF CLASSIFIERS AND ENSEMBLE-CLASSIFIERS USING THE COPELAND INDEX.

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Inroads have been made in our understanding of the risks posed to human health and the environment by NPs but this area requires continuous research and monitoring. ML techniques have been applied to nanotoxicology with very encouraging results. In this research, categories of ML classifiers (rules, trees, lazy, functions and bayes) are compared using datasets extracted from the Safe and Sustainable Nanotechnology (S2NANO) database to investigate their performance in predicting Nano-Particles (NP) toxicity. Physicochemical properties, toxicological and quantum-mechanical attributes and in vitro experimental conditions are used as input variables to predict the toxicity of NPs based on cell viability. Voting, an ensemble meta-classifier is used to combine base models to optimize the classification prediction of toxicity. To facilitate intercomparison, a Copeland Index is applied that ranks the classifiers according to their performance and suggests the optimal classifier. Neural Network (NN) and Random forest (RF) show the highest performances in the majority of the datasets. However, the combination of classifiers demonstrates an improved prediction resulting meta-classifiers to have higher indices.

O 24

AMPHIPHILIC POLY-N-VINYLPYRROLIDONE NANOPARTICLES FOR MEDICAL APPLICATIONS: INTERACTION WITH BLOOD COMPONENTS IN VITRO

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Polymeric nanoparticles have been widely used as one of the perspective types of drug delivery systems for several biomedical applications. Nano-scaled drug delivery systems can be applied by oral, transdermal, inhalation and injection administration. Once entering the circulatory system, nano-carriers will interact with blood cells and plasma proteins and can potentially run different pathophysiologic processes in the organism. Thus, for the investigation related to nanoparticle application in drug delivery, it is crucial to study nanoparticles behavior in blood.

However, the effect of polymeric nanoparticles on the cells and components of human blood is still not well investigated. When administered by injection as drug delivery system nanoparticles first of all interact with blood. Therefore, it is vital to study thoroughly the effect of nano-scaled drug carriers on human blood, and evaluate their blood compatibility. This work consisted in defining the in vitro behavior of amphiphilic poly-N-vinylpyrrolidone (Amph-PVP) nanoparticles toward the whole blood, blood plasma and blood cells in order to give assessment of nanoparticles blood compatibility. Amph-PVP nanoparticles were formed by self-assembling in aqueous media and composed of hydrophobic core and hydrophilic PVP outer shell known to decrease the recognition of nanoparticles by the blood components and immune system. The blood compatibility was evaluated by investigating influence on RBCs, WBCs, PLTs and complement system activation. These experiments were carried out on Amph-PVP nanoparticles, made of polymers with different molecular weight of PVP block (2000, 4000, 8000 Da), which had spherical shape, 60-100 mn size, and slightly negative surface charge. Our results demonstrated that Amph-PVP nanoparticles are rather stable in presence of blood serum, have no significant effects on the function of RBCs, WBCs, PLTs and complement system. Amph-PVP nanoparticles didn't show any considerable hemolytic and inflammatory effect, as well as influence on platelet aggregation, coagulation process, or complement activation at tested concentration range of 0.05-0.5 mg/ml.

Taken together, our investigations provide an overview of Amph-PVP nanoparticles in vitro blood biocompatibility. Through this work we present selected conditions of hemacompatibility and safety of Amph-PVP nanoparticles as an option for their further investigation as drug delivery system for biomedical applications.

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O 25

AMPHIPHILIC OLIGOMERS OF ACRYLIC ACID AS CARRIERS OF WATER-INSOLUBLE BIOLOGICALLY ACTIVE SUBSTANCES

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A number of acrylic acid amphiphilic oligomers in the presence of various long-chain mercaptans has been synthesized by radical polymerization. The structure of the isolated products was characterized by 1H NMR, 13C NMR spectroscopy, IR and electron spectroscopy. The determination of the number average molecular weight was carried out by end groups analysis, as well as critical aggregation concentrations (CCA). The regularities of changes in the CCA with varying the length of the hydrophilic and hydrophobic blocks of the synthesized oligomers, as well as the pH of the medium, were established. The ability of the synthesized oligomers to conjugate a number of biologically active substances in aqueous media, including protionamide, auxin and cytokinin plant growth regulators, has been determined. The resulting patterns can be useful in the development of new systems for the controlled delivery of these biologically active substances.

The kinetics of radical polymerization of acrylic acid was investigated, it was shown that the order of the monomer is 1.6. This observation is explained by the participation in the chain growth of both the monomeric form of acrylic acid and its associates stabilized by the formation of a hydrogen bond. The acceleration of the acrylic acid radical polymerization in 1,4-dioxane initiated by AIBN with the addition of mercaptans is noted. Probably, this effect is associated with the participation of mercaptans in the decay of the initiator. The obtained kinetic laws of the radical polymerization of acrylic acid were described quantitatively, the kinetic parameters of chain growth were determined with the participation of the associated and monomeric forms of acrylic acid.

The protionamide solubilization products of amphiphilic polyacrylic acid were used for the manufacture of anti-tuberculosis bone cements, and the solubilization products of plant growth regulators will be subjected to detailed research to determine the prospects for application in agriculture. The work was supported by Mendeleev University of Chemical Technology of Russia. Project Number 006.

O 26

SCREENING OF BIOPOLYMERIC MATERIALS FOR CARDIOVASCULAR SURGERY TOXICITY—EVALUATION OF THEIR SURFACE RELIEF WITH ASSESSMENT OF MORPHOLOGICAL ASPECTS OF MONOCYTE/ MACROPHAGE POLARIZATION IN ATHEROSCLEROSIS PATIENTS

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The successful development of technologies in regenerative medicine is largely associated with the development of biocompatible materials. The evaluation of the "toxicity" of the surface relief acquires particular significance for materials for cardiovascular applications, specifically, which are planned to be used as coatings for vascular stents, in patients with ichemic heart desease thanks to their tighter contact with blood and vessel wall and mass of their use. Macrophages (MPh) is one important cell class of blood, which necessarily interact with the implant. As a result of contact interaction with the material, polarization of MPh forms a new microenvironment for progenitor cells and realizes the processes of target histogenesis, which are good observed in model systems in vitro, are not always adequately implemented in vivo.

The morphotypes of human macrophages (MPh) were studied in the culture on nano-structured biopolymer substrates, made from polyhydroxyalcanoates (PHAs) of five various monomer compositions, followed by the solvent evaporation. Its surface relief, which was further in direct contact with human cells ***in vitro,*** was analyzed by atomic force microscopy (AFM) and scanning electron microscopy (SEM). It was shown, that the features of the micro/nano relief depend on the monomeric composition of the polymer substrates. Monocytes (MN) of patients with atherosclerosis and cardiac ischemia, undergoing stenting and conventional anti-atherosclerotic therapy, were harvested prior and after stenting. MN were isolated and cultured, with the transformation into MPh in direct contact with biopolymer culture substrates with different monomer composition and nano-reliefs, and transformed into MPh, in comparison with the same process on standard culture plastic. Sub-populations of cells with characteristic morphology in each phenotypic class were described, and their quantitative ratios for each sample of polymers were counted as an intermediate result in the development of "smart" material for cardiovascular devices. The results obtained allow us to assume, that the processes of MPh differentiation and polarization ***in vitro*** depend not only on the features of the micro/ nano relief of biopolymer substrates, but also on the initial state of MN ***in vivo*** and general response of patients.

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O 27

STUDY OF THE MECHANISM OF FREE RADICAL REACTIONS CATALYZED BY THE COMPLEX OF CYTOCHROME C WITH ANIONIC LIPIDS (CYT-AL) IN CELL MEMBRANES AND MITOCHODRIA

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The study showed that the nanoparticles of cytochrome c complex with cardiolipin (Cyt-CL) do not bind to erythrocyte or mitochondrial membranes. In contrast, free cytochrome c (CytC) is readily associated with both intact mitochondria and membranes of shocked mitochondria. These facts can be explained by the hypothesis that a positively charged CytC molecule is attracted by a lipid bilayer and penetrates into it, while Cyt-CL nanospheres, which have a predominantly negative charge in aqueous solutions due to excess of negative charges on cardiolipin (CL) molecules over positive charges of the CytC molecule, are repelled by cell membranes or mitochondria and are do not bind to them. Due to thermal motions of molecules, the absence of binding does not fully stop CytC from catalyzing the formation of lipid radicals in membranes, but it significantly reduces it.

This hypothesis was confirmed in experiments on formation of lipoperoxyl radicals in erythrocyte membranes, isolated mitochondria and mitochondrial membranes, carried out using the chemiluminescence kinetics method and mathematical modeling of the observed reactions.

In the course of these studies, it was found that usage of chemiluminescence enhancers, such as coumarins C-525, C-334 and C-314, is complicated by the fact that they can be a substrate of the peroxidase reaction. Therefore their concentration decreases during the measurements, and it is necessary to make an appropriate correction when estimating the reaction rates.

Along with the study of binding of Cyt-AL complexes and the enzymatic reactions that they cause, preliminary studies were conducted on the effect of Cyt-CL complex on cancer cell cultures. Conditions were selected under which it was possible to carry out a differential assessment of cytotoxic and apoptogenic effects, as well as the activation of lipid peroxidation reactions in cytoplasmic membrane under the action of Cyt-CL. Finally, it was shown that Cyt-AL complexes catalyzing lipoperoxidase reactions can be formed not only with CL, but also with another anionic lipid, phosphatidic acid.

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O 28

DEVELOPMENT OF 3D IN VITRO TUMOR MODELS FOR ANTICANCER DRUGS TESTING

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Tumor spheroids are a complex 3D cell culture model that reproduce in vitro some features of solid tumors in vivo, including oxygen supply limitations, the composition of extracellular matrix, secretion of soluble mediators, and drug resistance mechanisms. As a result, tumor spheroids are often used as an advanced in vitro model for tumor biology research and screening novel anticancer drugs. In the current research, we propose tumor spheroids as an advanced in vitro model for drug testing. For this purpose, co-culture system of melanoma cells and normal cells (fibroblasts, adipose-derived mesenchymal cells) has been developed and proposed to study the efficacy of metformin-based therapy of melanoma. However, the use of 3D cultures for the anticancer drugs screening requires reliable techniques to analyze cell viability. For this purpose, we have developed a novel electrochemical technique based on functionalized nanoelectrodes for label-free and real-time analyses of the microenvironment inside tumor spheroids. We introduced nanoelectodes into the spheroids and detected the changes in the oxygen and pH levels in function of the distance from the spheroids surface. Thus, we have found the decrease of oxygen levels from 240±20 μM to 120±20 μM when the nanoelectrode was introduced to a depth of 100 μm. The pH level also decreased and reached pH 6.5-6.6 in the spheroids core. These data are in a good agreement with previously published data about the spheroids internal structure. However, unlike the classical approaches (cytohistology, fluorescent dyes, microelectrodes), the proposed technique avoids severe damage to cells. As a result, it could be a perspective tool for real-time monitoring of 3D cell culture metabolites, both for the cancer biology study and for study the efficacy of antitumor drugs. The work was carried out with financial support from the Ministry of Education and Science of the Russian Federation in the framework of Increase Competitiveness Program of NUST MISiS (No. K42018052) and was also supported by RFBR, research project No. 180401087 (in part of spheroids formation)

O 29

STUDY OF THE INFLUENCE OF CELLULOSE PRODUCTION CONDITIONS ON ITS DISPERSED COMPOSITION

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Modified cellulosic materials, including nanostructured materials based on cellulose, occupy the most important place among individual types of biomaterials in terms of range and application possibilities. The unique properties of microcrystalline cellulose (MCC) make it possible to realize the possibility of modifying them, ensuring the creation of new materials with a complex of specified properties.

The actual problem is the establishment of the relationship between particle size, structure, and technological parameters of grinding equipment, allowing to create materials with new, technically valuable performance properties.

We investigated the dispersed composition of cellulose powders obtained on a modified extrusion unit. Flax fiber was used as a raw material for the production of cellulose powders. Cellulose powders were obtained by successively performing such operations as soda boiling of raw materials, physico-chemical activation of cellulose on a modified extrusion unit, washing the resulting suspension, drying and pulp grinding on a PM-120 rotary knife mill. Processing of pulp on the extrusion unit leads to its intensive grinding and defibrillation in the working cylinder of the extruder. This effect is achieved by cycling pulsating loads, which create high shear stresses that effectively act on the polymer chains of cellulose.

Installation for physico-chemical activation can contain up to 8 work units. The installation consists of a central screw and satellite screws that perform the function of grinding elements. In order to determine the optimal conditions for obtaining powders of cellulose from flax on a modified extrusion unit, the number of zones was varied, as well as the number and type of satellite screws.

The dispersed composition of cellulose powder samples, that obtained by physico-chemical activation, was determined using the method of continuous weighing of the sedimentation sediment on the CB-1 sedimentometer.

According to the results of the work, it was established that the type of work items (satellites) does not have a significant effect on particle sizes. Increasing the number of satellites to 7 allows to increase the yield of the smallest fraction of particles with sizes of 14-68 microns by about 10%. The most significant grinding effect is achieved when introducing additional zones of the extruder, and, as shown by the results of experiments, the use of more than two sections is impractical.

The research results were obtained in the framework of the state assignment 10.1718.2017/4.6.

O 30

THERMAL, MECHANICAL AND BIODEGRADATION STUDIES OF BIOFILLER BASED POLY-3-HYDROXYBUTYRATE BIOCOMPOSITES

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New methods of economic management should decrease the rates of consumption of nonrenewable fossil resources, preserving them for future generations. Industrial ecology and "green" chemistry are tools for creating new ecofriendly materials including those manufactured from renewable sources. Hybrids based on synthetic polyolefins and natural materials have been increasingly used in various applications. A new line of research is filling of microbial PHAs with natural materials to improve properties of the polymers and reduce their cost, in order to widen the range and increase the scale of their applications. This is particularly important for the large-scale use of PHAs in technical areas and agriculture. Biodegradable poly-3-hydroxybutyrate [P(3HB)] and natural materials (fillers) – clay, peat, and birch wood powder – were used to prepare powdered blends and, then, pellets and granules. Properties of initial P(3HB) and fillers and blends thereof were studied using IR spectroscopy, DSC, X-ray analysis, and electron microscopy. No chemical bonds between the components were revealed: the blends were physical mixtures. The degree of crystallinity of the blends was lower than that of the initial polymer, suggesting different crystallization kinetics of the blends. Introduction of increasing amounts of the fillers into the polymer progressively decreased mechanical strength of the pellets, as confirmed by the decrease in Young's modulus. The study of degradation of the blends in soil showed that the mass loss of the blends over 35 days of incubation in soil varied between 30 and 50% of the initial mass of the products, depending on the type of the filler. Thus, the blends prepared and tested in this study can be used to fabricate degradable packaging, greenhouse accessories, and delivery systems for fertilizers and pesticides.

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O 31

SYNTHESIS OF PHAS BY HYDROGEN BACTERIA IN A PILOT PRODUCTION PROCESS

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Polyhydroxyalkanoates (PHAs) – degradable polyesters synthesized by microorganisms as storage macromolecules – are promising "green" plastics. PHAs, which have a number of unique properties (biodegradability, thermoplasticity, processability by various methods), are justly considered materials of the 21st century. As raw carbon sources are responsible for about 40-50% of the PHA production cost, one of the conditions for successful commercialization of these polymers is expanding the range of feedstocks. The present study reports results of the biotechnological process of PHA synthesis by chemoorganotrophic hydrogen bacteria from various substrates scaled up to pilot production. Synthesis of homopolymer P(3HB) was scaled up to pilot production in a 150-L fermenter on sugars (fructose and glucose) and purified and crude glycerol in a two-phase batch culture of the wild-type strain Cupriavidus eutrophus B-10646. Over 60 h of cultivation, polymer content reached 85±5% on all carbon substrates, with cell concentrations differing insignificantly and with comparable consumption of carbon substrate. The highest cell concentration (X, g/L) was obtained on purified glycerol (160±10 g/L); the cell concentration in the culture on glucose was somewhat lower (150±10 g/L); cultivation on fructose and crude glycerol resulted in cell concentration of 130±10 g/L. Yield coefficients for the biomass on fructose, glucose, and purified glycerol were Yx 0.29±0.02; 0.32±0.02; 0.33±0.01 kg biomass/kg carbon substrate. Bipolymers [P(3HB/3HV) and P(3HB/4HB)] and terpolymers [P(3HB/4HB/3HV)] composed of major molar fractions of 3-hydroxybutyrate, 4-hydroxybutyrate, and 3-hydroxyvalerate and having a decreased degree of crystallinity (45-50%) and Mw 330-400 kDa were first synthesized in the scaled-up process using C.eutrophus B-10646 cultivated on glycerol supplemented with accurately dosed valerate and γ-butyrolactone. Substitution of glycerol for sugars reduced the cost of carbon substrate by 20-35%, depending on the degree of purity of glycerol. These results will provide the basis for scaling-up PHA synthesis in organotrophic C.eutrophus B-10646 culture.

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O 32

LIPOSOMES FOR TARGETED ANTICANCER DRUG DELIVERY: SYNTHESIS AND EVALUATION IN 3D IN VITRO MODEL

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The aim of the study was to develop an universal liposomal anticancer drug delivery system based on lipopeptides. Lipopeptides could be easily synthesized according to the optimized scheme with minimum technological steps and quickly adapted to desirable modifications of the delivery system. The system should: a) implement the targeted delivery of any encapsulated drug; b) be easily modified to vary delivery options (active or passive targeted drug delivery, delivery with controlled/sustained drug release). To reach the goal, "step-by-step" lipopeptide synthesis based on natural amino acids and long-chain alcohols was optimized. Lipopeptides which are able to form stable cationic liposomes with a desired size were selected and synthesized. The possibility of the cationic liposomes to effectively encapsulate both hydrophilic (doxorubicin) and lipophilic (thymoquinone) drugs as well as genetic material (siRNA) was demonstrated. As a result, a delivery system with prolonged drug release (cerasomes) and a system for active targeted drug delivery (folate-associated liposomes, FLPs) were developed. More over, a system with controlled drug release, namely magnetic liposomes (MLPs) were elaborated. All liposomes were characterized in terms of their physical properties (mean diameter, zeta-potential, storage stability, etc). The cerasomes were shown to have higher stability (>120 days) compared to that of conventional liposomes (10 days). The cerasome cytotoxicity as well as accumulation efficiency was studied in vitro using MCF-7 cells in 2D model (monolayer culture) and 3D model (tumor spheroids). MLPs were studied in terms of the drug release under non-heating low-frequency alternating magnetic field. By varying parameters of the magnetic field (frequency, intensity, exposition time etc) it was possible to cause the magnetite nanoparticles movement within a liposomal bilayer, and, as a result, to provide MLPs destruction and drug release. The FLPs were obtained using two approaches, namely by a classical thin film hydration technique, and by a new post-modification method. A batch of FLPs was studied in terms of their cytotoxicity and accumulation efficiency using MCF-7, C6, MSC and U-87MG cells, which are known to differ in folate receptor expression levels. The FLPs were shown to accumulate in the cells with folate receptors overexpression (C6, MCF-7) much faster compared to conventional liposomes without folate ligands. The uptake levels of FLPs and conventional liposomes by the cells with low folate receptor expression (U-87MG, MSC) were similar.

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O 33

CALIBRATED SPHERICAL MICROPARTICLES FOR EMBOLIZATION OF THE VASCULAR BED ON THE BASIS OF POLYVINYL ALCOHOL HYDROGELS

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One of the effective methods of treatment various pathologies, including hypervascularized neoplasms, is intravascular embolization. For this method, different types of medical devices are used, such as embolizing coils, uncalibrated microparticles, calibrated microparticles, non-adherent liquid embolizing systems, and adhesive compositions.

Calibrated spherical microparticles have high efficiency and relative ease of use and are used for embolization of uterine fibroids, prostate adenoma, arteriovenous malformations, hemangiomas, as well as for preoperative embolization and hemorrhage.

According to 2013, diverse types of calibrated foreign-made microparticles were presented on the Russian market. But due to the current difficult situation in the Russian economy and the imposed sanctions, after the events of 2014, there are difficulties with the import of a number of goods, including medical products. In the new reality, the main limitation for wider use of calibrated microparticles is their rather high cost - today the cost of a bottle containing 2 ml of particles is 20-25 thousand rubles as of March 20, 2019.

In connection with the above, this work is devoted to the development of technology for producing spherical calibrated particles based on unsaturated polyvinyl alcohol derivatives. Previously, this material has shown its effectiveness as a basis for a number of medical products, in particular wound dressings and implants for replacing soft tissue defects.

Polymer particles were obtained in a suspension consisting of a dispersion medium, which was n-butyl acetate, and a dispersion of frozen aqueous solution particles of an unsaturated polyvinyl alcohol derivative. The necessity of carrying out the process at temperatures below the crystallization of water is due to physicomechanical factors. In addition, carrying out the process under conditions of cryostructuring allows to obtain porous particles with high specific surface.

By varying the process conditions conditions were found that make it possible to obtain particles with basic sizes used in modern clinical practice from 100 to 1100 mm.

The next stage of work was toxicological and sanitary-chemical studies of samples of the obtained polymer particles. And also studied the nature of their interaction with blood. Studies have confirmed the high biocompatibility and hemocompatibility of the obtained polymer particles, which makes possible their potential use in medical practice.

O 34

MACROPOROUS POLYMERIC HYDROGELS FOR THE REGENERATION OF THE SPINAL CORD

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Severe spinal injury, complicated by damage to the spinal cord in the form of squeezing, crushing, partial or complete rupture, remains one of the urgent medical and social problems of modern medicine, because it leads to deep disability of the victims. The frequency of occurrence of this type of injury in different countries ranges from 11 to 112 people per 100,000 inhabitants.

It is advisable to use various polymeric materials as a growth direction "guide" for nerve fibers in the reconstruction of the spinal cord, specifically such a class of materials as porous hydrogels based on biocompatible polymers. Provided a number of technological conditions are met, the structure of such materials can contain a system of uniaxially oriented pores, which can act as growth pathways in the growth of axons.

In the current work, such hydrogels were obtained by cross-linking of solutions of unsaturated derivatives of polyvinyl alcohol in the cryogenic conditions. The uniaxial orientation of the pores was achieved by creating a temperature gradient during freezing.

The method of microsurgical reconstruction of the spinal cord using hydrogel was developed on animal material (cats).Surgical access to the lower thoracic region of the spinal cord was carried out, laminectomy of the Th10-Th12 arch was performed.

Further, the dura mater was opened and a microsurgical hemisection of the spinal cord was performed at the lower thoracic level with the formation of 10mm diastase between the distal and proximal ends. After that, a fragment of the hydrogel was implanted in the defect area.

Dynamic monitoring of animals lasted for 16 weeks. After 8 weeks after the intervention, separate movements in the affected limb were noted.

By the period of 10-11 weeks after the operation there was a restoration of strength to the level of 3 points (the possibility of leaning upon the affected limb).

After the end of the observation period, euthanasia of the animal and collection of material for histochemical studies were carried out, which showed the germination of myelin fibers through the hydrogel.

The results obtained in the experiment will allow to apply this method in clinical practice during reconstruction human spinal cord.

O 35

APPROACHES OF CANCER THERAPY BASED ON INDUCING OF APOPTOSIS AND FERROPTOSIS

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The effect of current anticancer therapies mostly is based on the stimulation of programmed death in cancer cells. One of them is apoptosis. But in cancer cells, and especially in those resistant to the action of various drugs, apoptosis is inhibited. Since mitochondria play a key role in triggering cell death, a treatment strategy aimed at influencing mitochondria may be promising in the treatment of cancer. It is assumed that intracellular delivery of cytochrome c can initiate apoptosis in cancer cells, bypassing factors that block the release of its own CytC from mitochondria. In order to effectively initiate apoptosis in cancer cells, various schemes had been developed for targeting drugs and drug delivery systems directly to the intracellular organelles responsible for the apoptosis initiating. Recently, we proposed a new approach to the initiation of apoptosis in cancer cells – by using cytochrome c nanocomplex with mitochondrial phospholipid – cardiolipin (Cyt-CL) to initiate peroxidation reactions in mitochondrial membranes. We showed the apoptogenic and cytotoxic action of Cyt-CL on different cancer cells in culture. Thy further Investigation in this direction may help to develop the strategy to induce apoptosis in drug-resistance cancer cells.

Another type of programmed cell death, most recently discovered, is ferroptosis. A plethora of research work has outlined the blueprint of ferroptosis as a new option for cancer therapy. One of the main features of it is total lipid peroxidation. Specific and selective oxidation of arachidonoyl- and adrenoyl-phosphatidylethanolamines in the 15th position of esterified acids by lipoxygenases navigate cells to ferroptosis. Further investigation of the mechanism of ferroptosis, especially with using high-resolution chromate-mass spectrometry, could help to disclose the mechanisms and regulate the ferroptotic death pathways with the purpose to eradicate cancer cells resistant to pro-apoptotic stimulation.

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O 36

TOXIC EFFECTS OF THE FUNGICIDE TEBUCONAZOLE ON FUSARIUM-INFECTED WHEAT PLANTS

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Fusarium infection is one of the most common diseases affecting cereal crops. The crop losses of maize, wheat, and rice affected by fusarium infection are economically important, as they are major sources of plant protein and their yields constitute over 55% of the total yield of cereal crops. Application of fungicides decreases the incidence of fusarium infection and reduces the levels of mycotoxins in commercial grain. Triazole fungicides now constitute 30% of the marketed fungicides. However, triazole fungicides, including TEB, are phytotoxic. The mode of action of the triazole group is to suppress ergosterol biosynthesis, preventing the formation of cell membranes, causing the death of pathogens. Thus, Fusarium-infected crops treated with triazole fungicides are adversely affected by two factors: Fusarium infection and fungicide. The present study investigates toxic effects of the fungicide tebuconazole (TEB) on Fusarium-infected wheat (Triticum aestivum) plants based on the morphological characteristics of root apices and changes in integrated parameters of redox homeostasis, including the contents of free proline and products of peroxidation of proteins (carbonylated proteins, CP) and lipids (malondialdehyde, MDA) in roots. In two-day-old wheat sprouts infected by Fusarium graminearum, the levels of proline, CP, and border cells of root apices are higher than in roots of uninfected sprouts by a factor of 1.4, 8.0, and 3, respectively. The triazole fungicide tebuconazole (TEB) at concentrations of 0.01, 0.10, and 1.00 μg/ml of medium causes a dose-dependent decrease in the number of border cells. The study of the effects of TEB and fusarium infection on wheat plants in a 30-day experiment shows that the effect of the fungicide TEB on redox homeostasis in wheat roots varies depending on the plant growth stage and is significantly different in ecosystems with soil and plants infected by Fusarium phytopathogens. The study of the morphology of root apices shows that toxic effects of TEB and fusarium infection are manifested in destructive changes in root apices and degradation of the root tip mantle.

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O 37

MODIFIED COPOLYMERS OF MALEIN ANHYDRIDE WITH DIFFERENT FUNCTIONAL ACTIVITY

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New approaches to the synthesis of biologically active, biodegradable macromolecular systems with antiviral, anti-inflammatory, anti-bacterial and hemostatic effects, stimulating the growth and development of plants, by modifying maleic anhydride copolymers with mono- and polyfunctional organic compounds containing oxygen atoms, nitrogen, and phosphorus have been implemented.

Polymeric anionic hydrogels with adjustable hydrophilicity and degree of crosslinking were synthesized by covalent binding of a copolymer of styrene and maleic anhydride (StMA) with polyhydric alcohols. The complex of physico-chemical methods established the features of the formation of the three-dimensional structure of the networks. The sorption properties of hydrogels and materials based on them were studied. New sorbing materials have been developed as a means for anterior tamponade of the nasal cavity, for stopping bleeding from the Kisselbach area and after rhinological operations. Comparative analysis of the clinical efficacy of tampons showed the advantageous aspects of its use. Hemostasis due to the release of aminocaproic acid from the structure of the tampon occurs in a shorter time in 1.5-2.5 minutes.

Immobilization of piperidol derivatives on the StMA macromolecule obtained polymeric water-soluble forms of biologically active substances (BAS), plant growth and development stimulants effective for a wide range of crops. Polymeric forms of BAS surpass their low molecular weight analogs. The drugs have been tested for acute toxicity and cumulativeness. The drugs are practically non-toxic, have low stimulating concentrations, have a prolonging stimulating effect.

Modification of the StMA copolymer with humic acid synthesized polymeric water-soluble BAS, that stimulate the growth and development of plants, increasing the resistance of plants to stressful situations. Processing plants with potato solutions of drugs activates the germination of tubers, accelerates the emergence of seedlings for 3-4 days, the plants enter into budding and flowering earlier, yield compared to their monomeric form increased by 12%.

Biodegradable complex nonionic surfactants are obtained by modifying the StMA copolymer with polyhydric alcohol esters (Tween-85). The patterns of catalytic esterification are revealed, the structure and composition of polymers are studied. The developed NSA are effective reagents for field preparation of oil to commercial quality and transport of high paraffin oils. With the consumption of reagents from 100 to 200 ppm, the depression amounts to 18-22°C, the degree of inhibition of paraffin wax reaches 78%, the degree of protection against corrosion exceeds 60%.

O 38

NEW NANOSCALE POLYMERIC SYSTEMS FOR ANTICANCER THERAPY

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Amphiphilic derivatives of water-soluble polymers, in particular, poly-N-vynilpyrrolidone, are of a great interest as a drug carriers. Amphiphilic poly-N-vynilpyrrolidone was prepared by radical polymerization with chain transfer agent alkylthiol type. The synthesized polymers are capable of spontaneous aggregation in aqueous medium with formation of nanoscale micelle-like particles. It was shown that critical micelle concentration depends on molecular weight of polymer and length of alkyl fragment. Such systems can be used as a carriers of poorly or water insoluble substances, such as most of anticancer drugs. Amphiphilic poly-N-vynilpyrrolidone proved to be suitable for use as carrier of 5-Fluorouracil (5-FU) and paclitaxel. Studies have been conducted on the incorporation of anticancer drugs in nanoscale aggregates of amphiphilic polyvinylpyrrolidone. Using the methods of dynamic light scattering and TEM, the dependence of the particle size on the preparation method and the molecular weights of the polymer and anti-cancer drug itself has been studied. Using the example of 5-FU, it was shown that the use of a polymer as a carrier envelope critically affects. Use of pure 5-FU leads to an accumulation of neutrophil extracellular traps in the blood, which cause various complications. It was shown that with the introduction of 5-fluorouracil immobilized in polyvinylpyrrolidone nanoaggregates, the number of generated neutrophil traps is significantly reduced.

O 39

RECOMBINANT BACTERIOPHAGE ENDOLYSIN LYS394: LYSIS E.COLI UNDER ULTRALOW-FREQUENCY ALTERNATING MAGNETIC FIELD IN THE PRESENCE OF MAGNETIC NANORODS

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Endolysins are enzymes used by bacteriophages at the end of their replication cycle to degrade the peptidoglycan of the bacterial host from within, resulting in the cell lysis and release of progeny virions. These lytic enzymes confer a high degree of specificity and could potentially replace or be utilized in combination with antibiotics, with the aim to specifically treat infections caused by bacterial pathogens. However, the activity of endolysins against gram-negative bacteria is limited because the outer membrane in the latter acts as a physical barrier and prevents endolysin from accessing the peptidoglycan from outside.

The effectiveness of endolysins active towards gram-negative bacteria can be increased by destabilizing the outer membrane in the latter. Theoretical studies of the interaction of functionalized magnetic nanorods (MNR) with a biological membrane have shown that the action of ultralow-frequency alternating magnetic field (AMF) can dramatically change membrane permeability.

The purpose of the work presented was to study the effect of ultra-low frequency AMF on the outer membrane of E. coli cells interacting with functionalized by dopamine magnetite MNRs (40x10 nm). Electrostatic interactions take place between positive charge of dopamine and negative charge of phosphate groups of lipids. Complex oscillating movements of MNRs occur under AMF application. In this case, oscillating forces and deformations with normal and lateral components appear in the membrane. It was found out that bacteriophage S394 endolysin can significantly increase its catalytic activity in the E. coli cell wall lysis in the presence of MNRs under AMF exposure. Changes in membrane permeability under AMF action (membrane destabilizing effect) have been confirmed by two independent experiments. In the first one, β-lactamase release from E. coli cell periplasm was revealed upon magnetic field application. As shown, 75% of β-lactamase could be measured in supernatant of cell suspension after AMF application. In the second experiment, the hydrophobic dye Nile Red capable of fluorescing exclusively in nonpolar media was used. As found, the fluorescence intensity of Nile Red sharply decreased ten times upon AMF application. It worth mentioning that fluorescence was coming back after AMF was stopped reaching the initial intensity within 5-10 min (reversible membrane permeability change).

Thus, the conducted study demonstrates the prospects of using external ultralow-frequency AMF in enhancing the action of antibacterial bacteriophages endolysins against gram-negative pathogens.

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DEVELOPMENT OF NEW IMPLANTABLE BONE GRAFTS WITH RHBMP-2 AND ERYTHROPOIETIN FOR RECONSTRUCTIVE SURGERY

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Development of new materials for reconstructive surgery is one of the key problems among the priority scientific areas of rehabilitation, regenerative and adaptive medicine. The use of non-resorbed implantable materials is required to replace large bone defects. Promising in this regard are such synthetic materials as ultrahigh-molecular polyethylene (UHMWPE) and polyetheretherketone (PEEK). To improve the fusion of implants with bone tissue, the possibility of their joint application with recombinant proteins having osteogenic properties is relevant.

We used porous variants of UHMWPE and PEEK activated by hydroxylapatite (HA) introduced into their structure in combination with recombinant BMP-2, erythropoietin or both proteins to study osteogenicity in the model of cranial critical-sized defects (CSD) regeneration in mice.

The recombinant proteins used were rhBMP-2 and erythropoietin proteins with additional protein domains providing improvement of solubility and ability to self-induced binding to the carrier. Both recombinant proteins are capable to spontaneous sorption on hydroxylapatite (HA).

The study was carried out on 45 outbred male ICR (CD-1) mice of 38-47 days old. Animals were distributed into 9 groups, 5 mice per group. UHMWPE/HA and PEEK/HA disks of 1.0 (thickness) x 4.0 (diameter) mm with/without bound proteins were sterilized and implanted into 4 mm CSD of mice. In group 1 (control) CSD were empty; in groups 2, 3 CSD were filled with the UHMWPE/HA and PEEK/HA disks (respectively); in groups 4, 5 CSD were filled with disks containing rhBMP-2; in groups 6, 7 CSD were filled with disks containing erythropoietin; finally, in groups 8, 9 CSD were filled with disks containing both rhBMP-2 and erythropoietin. Tomography was carried out on 0, 3, 6 and 9 weeks post-surgery; eutanasia and histomorphometry were performed on 60 day after surgery. According to the results of tomography and histological analysis all implanted biocomposites demonstrated their high biocompatibility. The addition of rhBMP-2 to the scaffolds resulted in significant osteogenic effect and formation of large mineralization areas within 3 weeks after surgery. The addition of erythropoietin led to an increase in the quality of the newly formed bone tissue, as well as, in some cases, to an increase in the amount of mineralized bone.

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O 41

TARGETING CXCR4 WITH IMMUNO-MODIFIED IRON OXIDE NANOPARTICLES FOR CANCER TREATMENT WITH MAGNETICALLY-INDUCED HYPERTHERMIA

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Magnetic hyperthermia (MHT) therapy is a cancer treatment that takes advantage of the ability of magnetic nanoparticles (MNPs) to produce heat when exposed to an alternate magnetic field (AMF). The overexpression of the chemokine receptor, CXCR4, in a range of cancer cells, namely brain tumour, glioblastoma (GBM) and leukaemia, among others, has been related to tumour development, growth and metastasis, making CXCR4 an appealing target for cancer diagnosis and treatment. Particularly, CXCR4-targeted magnetic nanoparticles (MNPs) have been tested for cancer diagnosis, but still have not been used for cancer treatment.

With the above rationale in mind, it was our purpose to functionalize MNPs with antibodies (targeted particles) to produce MHT in cancer cells with elevated efficiency while presenting low toxicity in normal cells. For this purpose, we optimized the covalent binding of biomolecules to poli(acrylic) acid- (PAA) coated superparamagnetic iron oxide nanoparticles (SPIONs), using BSA as model protein. For studies with cells, the acute lymphoblastic leukaemia in vitro model, Jurkat cell line, was initially tested for the implementation of the methodology due to the wide expression of CXCR4 receptor. Subsequent studies were performed in a GBM in vitro model that expressed intermediate levels of CXCR4 receptor and has been previously used for testing other GBM treatment options. Cells from human kidney (HK-2 cell line) were used as negative control. For the optimized MHT strategy, dextran-coated, cluster type, 250 nm particles (MPs), with PAA at the surface, were used, after functionalization with anti-CXCR4 antibodies (targeted MPs, MP–CXCR4). The efficacy of the targeted MPs to induce cytotoxic MHT in the selected in vitro models was studied and tuned, seeking to enhance the observed effects of targeted MHT, while keeping a mono-therapeutic scheme.

The studies on Jurkat cells showed that a purely CXCR4-targeted approach underperformed in the MHT studies, resulting in limited toxicity in cancer cells. The efficiency of this approach was then enhanced by providing cells with a boost of magnetic material of a non-targeted origin (SPIONs). The cells internalized a sufficient amount of SPIONs to increase the magnetic material, and producing heat after optimized AMF application during 1 h. This way, remarkable effects in cell viability were observed, following two distinct death pathways, according to the temperature reached and kept during MHT. This strategy was subsequently applied to a GBM in vitro model, which needed an improved boost of SPIONs due to lower surface expression of CXCR4 receptor. Again, the MHT treatment established herein resulted in long-lasting, null cell viability, and only features of a necrotic signature were observed. Furthermore, the developed strategy proved to be safe for control HK-2 cells.

Overall, the combination of targeted and non-targeted nanoparticles for MHT resulted in remarkable toxicity in cancer cells, while keeping normal cells nearly undamaged. This strategy is a rare example of efficient MHT in a mono-therapeutic context, proving interesting and promising for future in vivo studies.

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TOXICITY OF GOLD NANOPARTICLES IN 4T1 AND A2780 PGL451 CELL LINES.

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Nanoparticles (NPs) are defined as particles having all dimensions of 100 nm or less. Metallic NPs are used in an increasing number of applications in industry, science and medicine. Among metallic NPs foreseen to be widely used in medicine are gold nanoparticles (AuNPs) due to their low toxicity. AuNPs are used for diagnostic and therapeutic purposes, including biosensor applications, targeted delivery of anticancer drugs, bioimaging of cells and tissues, photo-thermal agents.

The aim of this study was to investigate cytotoxicity and genotoxicity of AuNPs in two cell lines: human ovarian carcinoma A2780 and murine mammary carcinoma 4T1. Both cell lines were exposed to AuNPs in concentration range of 5-100 µg/ml for 24 or 48 h and the cytotoxic effect of AgNPs was measured by the resazurin assay. AuNPs-induced production of ROS was investigated by flow cytometry as oxidation of H2DCFDA in cells treated with NPs in concentration 10, 50 µg/mL for 2 h. Finally, genotoxicity was measured by the comet assay.

As expected, AuNPs were non cyto- or genotoxic for both cell lines in the range of tested concentrations. Interestingly, the highest tested AuNPs concentration induces a moderate ROS production, apparently without any consequences for cell survival or induction of oxidative damage to DNA. Among the two lines tested, production of ROS was more intense in A2780 cells in 4T1 cells.

In conclusion, despite the moderate induction of ROS production AuNPs were non toxic for both cell lines.

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STRENGTH AND FATIGUE OF NATURAL AND ARTIFICAL MATERIALS

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Material strength is a complex concept that includes the material resistance to various types of loading. Often the improvement of strength in one type of load leads to deterioration in the other. For example, the ordinary window glass is quite durable material under the pseudostatic slow loading, but it is easily broken upon impact. In solid mechanics, there are conceptions of the static strength and fracture toughness characterizing resistance to the crack growing in a material. The glass has very low fracture toughness: a crack propagates easily in it. Metals can possess both high strength and high fracture toughness. These characteristics are largely determined by the possibility of dislocations movement. The easier the dislocations move, the lower the static strength, but the higher the fracture toughness, the harder the crack propagates. Therefore, the introduction of special additives impeding the dislocations movement (for example, carbon in iron) leads to increase in the static strength, but also to rising in brittleness and facilitating the crack propagation.

The nature and human being, following to it, found a way out of this contradiction by creating composite fibrous materials such as wood or glass-reinforced plastic. In this case, a crack arising from a fiber break, encounters an adjacent fiber and turns along the fiber due to the large difference in the strength of the fibers (high) and the binder or interphase between them (low). Thus, a crack propagation across the loading direction becomes less dangerous, being located along the straining. This occurs when stretching of the unidirectional fibrous material along the along the fibers (the reinforcement direction). Selecting the desired reinforcement scheme, i.e. the different layers location depending on the external loading, the full-strength material can be got, which cannot be obtained from an isotropic material. Here is an example of a pipe operating at high internal pressure. In this case, the radial stresses are approximately twice the axial stresses. This means that a pipe made of an isotropic material (metal, polymer, ceramic) always bursts along the pipe generatrix due to the radial stresses. To protect a pipe in this case we should thicken its walls using too much material. From a unidirectional anisotropic material, we can construct an equal-strength structure by placing along the axis half as many layers as along the radius. In the same way we can design other, more complex parts, forming equal-strength products. This is an example of how can we use two different strength characteristics – the static strength and fracture toughness.

Another characteristic of the material strength –is the fatigue strength under cyclic bending. It is well known that the metal wire is broken readily after a few bending. The same thing will be happened, for example, with a plastic comb. The fact is that solids accumulate defects (dislocations in crystalline materials, dilatations in glasses, crazes in polymers, etc.) under large plastic deformations, . These defects turn into cracks leading to the material destruction. Unlike solids, in liquids, during defects are not accumulated with deformation (flow) or they quickly relax and the body returns to an equilibrium state. For large bending deformations of, say, bones, the nature invented a special "device" as articulations containing the liquid lubricant, which is able to support large deformations. Similarly, lubrication works in bearings.

The tree is especially interesting. The liquid juice in the living branches, apparently, takes over large bending deformations. If a tree or branch dries up, it becomes brittle and breaks easily when bent. At low temperatures, the liquid juice seemingly should freeze and the tree should become brittle. Yes it is truth. However, in such trees as larch, which can survive even at Siberian frosts, its juice is an aqueous solution of a polysaccharide (arabinogalactan), freezing at very low temperatures (eutectic). Elastomers and rubbers are other materials that do not accumulate defects during deformation. These materials are in the liquid state under normal conditions ($T > Tg$, T is the operating temperature, Tg is the glass transition temperature) and relaxation times of their structure are relatively small. The muscles of animals and humans or tires and other rubber products that man has created are arranged in the same manner.

O 44

SELECTION OF DNA APTAMERS BASED ON SEPARATION OF DNA–PROTEIN COMPLEXES FROM DNA LIBRARY USING DIFFERENT METHODS OF CAPILLARY ELECTROPHORESIS

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Screening molecular libraries for affinity ligands capable of binding protein targets is the mainstream approach for identifying drug leads. Random-sequence DNA (or RNA) libraries are screened for DNA (or RNA) aptamers that can bind proteins in solution or on the cell surface with high affinity and selectivity. A general approach for aptamer selection is systematic evolution of ligands by exponential enrichment (SELEX). SELEX is typically carried out with a protein target immobilized on the surface (e.g. of magnetic beads). Due to non-specific adhesion of DNA to the surface the separation is so inefficient and its multiple rounds are required to reach reasonable level of purification. In addition to being a very lengthy process the multi-round SELEX can only produce a limited number of unique aptamers and often completely fails. Our group has invented kinetic capillary electrophoresis (KCE), a solution-basedalternative to the surface-based approach for separating DNA–protein complexes from the unbound DNA library. One of the most popular KCE methods is nonequilibrium capillary electrophoresis of equilibrium mixture (NECEEM), in which DNA–protein complexes move ahead of the unbound DNA library inside the capillary. NECEEM offers efficiency of aptamer separation 103 times higher than that of surface-based methods and a capability of easily assessing the affinity of the selected aptamer pool. However, NECEEM has a limitation associated with the non-uniform migration pattern of DNA in electrophoresis which may lead to the overlap between the zone of DNA–protein complexes and that of the DNA library. Such an overlap limits the efficiency of NECEEM-based separation at 105 Our novel Ideal-Filter Capillary Electrophoresis (IFCE) method makes DNA–protein complexes move to the capillary output while sending the unbound library in the opposite direction [1]. The efficiency of IFCE-based separation was optimized by adjusting the ionic strength of the background electrolyte to reach an extremely high value of 109 This value is 107 times higher than the separation efficiency of surface-based methods. In the proof-of-concept work, we demonstrated that IFCE allowed unique one-step selection of a high-affinity aptamer pool to a protein target.

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BIOMONITORING OF LEAD IN A CHILDREN'S COHORT

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Lead (Pb) has been a constant concern for the public health around the world. Several efforts are developed for the regulatory Institutions since 70´s to reduce the exposure, especially to vulnerable population like children. A series of surveys to know the level exposure to their population, where lead is included as one of the pollutant of interest, are carried out in several countries.

In the present study lead concentration on blood was quantified during the Multiple Indicator Cluster Surveys (MICS) survey carried out in Georgia by UNICEF, Geostat and NCDC; the fieldwork was carried out from September to December 2018. The analysis was performed by the ICP-MS technique with a methodology accredited according to ISO/IEC 17025 by ACCREDIA (Italy). Briefly, an aliquot of 1000 µL of blood was digested using ultra-pure nitric acid and heat; the final analytical solution was obtained by diluting 1:5 v/v with ultra-pure water and by adding 100 ppb of indium as internal standard. Then, addition calibration was used to control for matrix effects during the instrumental analysis and the most abundant and relatively less interfered lead isotope was measured, i.e., 208Pb.

A total number of 1571 samples were analysed. Arithmetic mean value of 65.1 µg/L, min - max range of 6.78 - 518.5 µg/L and 50th – 95th percentiles at 46.3 - 187.4 µg/L were obtained. Lead-blood levels higher than in Georgian children are found in Nigeria's villages involved in gold ore processing and a children cohort from Egypt. However, the results for Georgia's children are in general significantly higher than other surveys. The Georgian reference value (RV) at 95th percentile is two or three times higher than that displayed for Greece, Italy or Canada as well higher than the RV established in Germany (GerES IV-2010, RV95: 33.8 µg/L) and USA surveys (CDC-2012, RV97.5: 50 µg/L). To date, German HBM-I and HBM-II values have been suspended as even low level exposure has been associated with adverse health effects, so, the current goal is to reduce exposure at the lowest level possible. For this reason, in the Georgian context a great challenge will be to evaluate the potential Pb sources, both indoor and outdoor, as first attempt to reduce their contribution.

P 01

APPLICATION OF CHITOSAN-POLYVINYL ALCOHOL FILMS FOR THE CONTROLLED RELEASE OF MEXIDOLE

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In the present study the application of chitosan-polyvinyl alcohol films for the controlled release of mexidolel for treatment age-related macular degeneration have been developed. Chitosan has a great potential for applications in ophthalmology due its biodegradability, biocompatibility, non-toxicity and versatile chemical and physical properties. Films of chitosan-polyvinyl alcohol blends in different compositions containing various doze of drug have been prepared by solution casting method from 5-10% solutions. Influence of various factors on process of drug release from films in conditions «in vitro» was investigated. It was shown that pharmacology active substance practically completely diffused in Ringer-Lock solution within 4-6 hours, not undergoing any changes. With increase in thickness of film process of drug diffusion is slowed down. The 50 % of drugs from system by thickness 0,3 mm was released for 2,5-2,8 h, but the same quantity of drugs by thickness of film 0,6 mm was diffused for 4,3-4,5 h. Coefficients of diffusion of released drugs have been calculated and is shown that with increase in thickness of the films in 3 times this parameter decreases approximately in 2 times. The profile of kinetic curves testifies that process of release occurs according to the first order kinetic and controlled by diffusion of the therapeutic agent in polymeric matrix. In according with Higushi equation, describing kinetic of drug diffusion from monolithic systems with the dissolved therapeutic agent, dependence of amount of diffused drugs from films versus root of square time had linear character. Values of the diffusion coefficients has appeared within the limits of 2,5-3,0x10-7 sm2/s for four concentration that testified to absence of significant influence of drug loading for rate release from films.

Polymeric biomaterials were used for treatment of age-related macular degeneration at 24 patients. The experimental and clinical tests show that implantation of films to suprahoroidal area did not cause the pathological changes in the membrane of eyes and help to activate the formation of vascular anastomoses in 1 month. The positive effect is prolonged up to 6 month in 63 %. The results obtained in the present work have shown the perspectives of use polymeric biomaterials based on chitosan-polyvinyl alcohol blends for prostaglandins delivery for application in ophthalmology for the treatment age-related macular degeneration.

P 02

RELEASE BEHAVIOR OF FLUOROURACIL FROM CHITOSAN-COATED CALCIUM ALGINATE MICROPARTICLES

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Alginic acid and it salts have found wide application in pharmaceutical practice as loosening and binding remedies upon the production of tablets and preparation of ointments and pastes. Alginic acid in the presence of divalent cations such as calcium ions forms microparticles as result from specific and strong interaction between cation and guluronic acid resudes. A strong structure of alginate gel and big sizes of pores allow one to easily immobilize large quantities of different drugs, proteins, enzymes and cells.

The purpose of present work is development of polymeric medicinal forms with the controlled action by immobilization anticancer drug fluorouracil on polymeric microparticles of calcium alginate. Microparticles were obtained in the following way: at the first stage a solution of drug in 2,5% solution of sodium alginate was prepared, then the obtained solution was filtered and syringed dropwise into 0,1 M calcium chloride at a constant dropping rate of 1,0 ml/min. The obtained microparticles of calcium alginate were treated by the solution of calcium chloride for 30 min, washed with distilled water and physiological solution. As a result microparticles of calcium alginate containing immobilized fluorouraci were obtained. For the determination of kinetics of drug release from alginate microparticles a special device was applied, consisting of a metallic basket, a thermostated glass and a mechanic mixer. The release of drug was studied under conditions in vitro at 37°C. With this purpose a definite quantity of alginate particles was placed in a metallic basket, immersed in 300 ml of thermostated physiological solutions at pH 7,1. A constant rate of mixing of the released medium (100 turns/min) was ensured with the help of a magnetic mixer, thermostating was maintained with the help of a running cell. After definite time intervals 2 ml of the solution was selected for the determination of the content of drug with the help of UV-spectroscopy. Release of drugs was controlled each minute for the first 10 minutes, each 2 min for the following 100 minutes.

The scanning electron micrographs of the dried fluorouracil-loaded alginate microparticles show at the presence of chitosan the microparticles had thicker surface and fewer folds than microparticles obtained without chitosan. For the study of polyelectrolyte complex formation between sodium alginate and chitosan in solution a conductometric and turbidimetric titrations were used. When an alginate drop falls into chitosan solution, the interphasic membrane is formed by complexation between two polyelectrolytes of opposite charge through electrostatic interaction. Calcium chloride in a chitosan solution diffuses into the alginate core more rapidly than chitosan because of its low molecular weight and forms a gel core. Subsequently, a microparticle of an alginate gel core coated with alginate/chitosan interphasic layer is formed. In weak acidic medium with pH of 4,8 the formation of polyelectrolyte complex of an equimolar composition takes place, which is testified by wider range of minimum value of running through of a solution with the content of alginate of 40–60 %. The results of our study indicate that there is great potential in designing microparticles of calcium alginate gel, modified by natural polymer chitosan, as carrier of antitumor drug fluorouracil . The use of such systems makes it possible to develop systems with required rate of drug delivery to the body in accordance with the pre-set time program.

P 03

MODIFICATION OF THE POLYSACHHIRIDE CAPSULES BY SILANIZATION

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Since different behavior of polymer ultrathin films silanization compare to the bulk materials was reported, the dynamics in nanoscale polymeric materials has been attracted particular attention. This subject is important for development of nanoscale materials for practical application in various fields. Currently, active work is underway to identify interesting features of polymer capsules under the influence of silanization.

In this research, the capsules were formed by emulsification of soy bean oil in the polymers solution applying a low frequency ultrasound treatment. The ultrasonication provides a spontaneous emulsification of the oil in the water polymers solution followed by formation of stable polymer shell on the surface of the oil droplets due to a cavitation process. The cavitation provides physic-chemical interaction between the polymer moieties creating the polymer shell of the capsules. The capsules were stable over months while keeping in the solution. However, they were collapsed under ambient open conditions.

To improve the stability of the capsules, we performed the silanization of their surface by tetraethoxysilane (TEOS) hydrolysis reaction. The resulted capsules were indeed covered with silica shell, which made the capsules more denser and stable on the open air.

The capsule morphology before and after the silanization was studied by scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM). The hydrophobic model fluorescent dye (Nile red) was encapsulated into the developed capsules to demonstrate the possibility for future encapsulation. The obtained results demonstrate that the proposed capsules can be thickened by silanization and used for encapsulation of various hydrophobic compounds.

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P 04

THE USE OF MACROPOROUS POLYMER HYDROGEL BASE ON POLYVINYL ALKOHOL IN THE TREATMENT OF EXTENSIVE SOFT TISSUE DEFECTS AFTER ABDOMINALPERINEAL EXCISION

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Currently, colorectal cancer is second among the most frequent malignant tumors of the gastrointestinal tract. Recently, there has been a tendency to increase the incidence of colorectal cancer. Today, various methods of complex and combined treatment of oncological diseases have been developed, however, surgical tactics remain a priority for the rectum. In 30 per cent cases, when a tumor is localized in the lower ampulla of the rectum, an extruding abdominoperineal excision is performed with a permanent colostomy forming on the anterior abdominal wall. The main disadvantages are the invasiveness of the operation, the formation of an extensive defect of the soft tissues of the perineum as a result of dissection, which leads to a large number of infectious complications and the formation of perineal hernias. Actually there are many techniques for closing the perineal wound, but none of them is fully accepted, due to positive and negative sides. One of the modern methods of tissue regeneration and repair is the use of macroporous polymer hydrogel based on crosslinked polyvinyl alcohol (PVA). This method was applied in an experiment in which PVA was implanted into the soft tissue of a rabbit in order to study the stages and timing of its biodegradation in soft tissues. Almost complete biodegradation of PVA and its replacement with connective tissue was observed by the end of 3 months after the implantation of the drug. In clinical work, PVA was used on two patients. In the first case after abdominalperineal excision bleeding from the perineal wound was noted in the postoperative period. The patient was re-operated, the sutures were removed, the wound was inspected, the bleeding stopped. Further the wound was conducted openly with the installation of PVA in it. The patient was discharged from the hospital with positive results on the 13th day. In the second case, after evisceration of the small pelvis into the perineal wound, PVA was also established with a positive result. Thus, the use of this technique is justified on patients with complicated postoperative wounds of the perineum.

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P 05

THE INFLUENCE OF SYNTHETIC STRATEGY ON THE POLY(4-OXYBENZOYL) PROPERTIES

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Poly(4-oxybenzoyl) is a wholly aromatic polyester (POB) known under the brand name Ekonol that could be attributed to liquid-crystalline polymers. To date, this class of polymers has received considerable attention due to the unique combination of properties: high-temperature stability, excellent mechanical properties, radiation resistance, low coefficient of thermal expansion, chemical resistance and so on. Therefore, POB polymers have been realized in the various industrial fields, such as self-lubricating materials and high-performance engineering plastics for electronics, machinery, aerospace, etc. A general synthetic strategy to POB involves the polycondensation of phenyl ester of 4-hydroxybenzoic acid (4-HBA), being used instead of free 4-HBA in order to prevent the side reactions, namely decarboxylation and etherification. Utilization of 4-acetoxybenzoic acid as a monomer is another successful synthetic path for POB oligomers. The selection of a particular monomer for polycondensation plays a crucial role in the molecular weight of oligomers and their morphology. In this context, it is worth noting that the attempts to synthesize the high molecular products from free 4-HBA have failed due to the aforementioned side reactions.

In this study, we report the preparation of POB oligomers from neat 4-HBA by high-temperature polycondensation in an inert solvent using transesterification catalyst. The same reaction conditions were used to obtain oligomers derived from phenyl ester of 4-HBA. In the first case, the polymerization was evidenced by the disappearance of the characteristic carbonyl stretching band at 1672 cm-1 and the appearance of C=O ester band at 1740 cm-1 together with the stretching vibrations corresponding to a terminal –COOH group at 1698 cm-1. The molecular weight of oligomers synthesized from neat 4-HBA, being determined by FTIR spectroscopy, was comparable with the ones obtained from phenyl ester of 4-HBA and varied in the range of 1500-4000. The WAXS results have revealed a highly ordered structure of the product obtained with about 13 significant peaks that were matching with the data from the literature. According to the thermogravimetric analysis, the oligomers were resistant to high temperatures up to about 350 °C. The activation energy of thermal decomposition, calculated using the Horowitz – Metger equation, for samples obtained from free 4-HBA was slightly lower than that of oligomers synthesized through ester formation stage.

P 06

WATER-SOLUBLE POLYMERIC FORMS OF PLANT GROWTH REGULATORS

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Plant growth regulators (PGR) have attracted serious attention since the 20s-30s of the last century, when the fundamental possibility of their use was shown, as well as synthetic analogs of PGR. Most of the complexity and limitations of the widespread use of PGR are associated with the characteristics of their properties: most PGRs show stimulating activity in a fairly narrow range of concentrations, the excess of which leads to inhibition and even death of plants. As is known, so-called systems with controlled release of the active substance are used to eliminate such deficiencies inherent in various PGR. Two ways to solve this problem were developed. The first is the copolymerization of allylamides with attached PGR (2,4-dichlorophenoxyacetic acid (2,4-D), naphthylacetic acid (NAA-1), benzyladenine) with acrylic acid. The regularities of the copolymerization process of acrylic acid and PGR's allylamide were established in relation to the effect of copolymerization time, total monomer concentration, process temperature, amount of initiator and composition of the monomer mixture, which allowed to establish optimal conditions for maximum yield, high content of active units and low viscosity of the copolymer. The second way to obtain polymeric forms of PGR was to incorporate them in nanoscale aggregates of poly-N-vinylpyrrolidone. Polyvinylpyrrolidone with a terminal octadecyl group was obtained by radical polymerization in the presence of a chain transfer agent - octadecyltiol. PGR was incorporated into the micelles in three ways: emulsion, dialysis and suspension. The laws of the PGR incorporation degree into aggregates and particle size were established depending on the preparation method and molecular weight of polymer. It was shown that the obtained water-soluble polymeric forms have a high growth-regulating activity, in contrast to their low molecular weight analogues.

P 07

THE INFLUENCE OF THE SIZE AND SURFACE CHARGE DENSITY OF LIPOSOMES ON THE PROPERTIES OF THEIR COMPLEXES WITH A MICROGEL

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Today, there are a large number of different physiologically active substances. However, most of them may never become drugs. One of the most common reasons that prevent the use of sometimes the most active compounds is the presence of undesirable side effects. Another equally important problem is related to the inability of many drugs to penetrate into the affected cells and tissues that are subject to therapeutic treatment.

One of the urgent problems at present is the development of stimulus-sensitive nanocontainers as a system for delivering cytostatics to the human body during chemotherapeutic treatment of cancer. To solve this problem, it is suitable to obtain and study the properties of stimulus-sensitive microgel complexes based on N-isopropylacrylamide, 3- (N, N-dimethylaminopropyl) methacrylamide, N, N-methylene-bis-acrylamide, and lecithin and phosphotidylserine.

The use of liposomes alone as a delivery vehicle has its drawbacks: they are not stable enough and are quickly cleared from the body by macrophages. For this reason, it is not possible to direct medicinal substances precisely to the organs and tissues where the pathological process takes place.

Microgels are a new class of polymer nanoparticles, especially interesting as delivery vehicles, as they are in the water in a swollen state and can hold various drugs inside themselves, from low molecular weight to biopolymers: proteins and nucleic acids. In addition, the use of appropriate monomers makes it possible to impart necessary properties to microgels, including such as thermal and pH sensitivity.

When the pH collapses and the thermosensitive microgel, the contents of adsorbed liposomes will be released into the external solution. The dynamic light scattering method was used to study the effect of the size of liposomes and their charge density on the properties of their complexes with a microgel, the stability of the complexes at different ionic forces. Using fluorescence spectrophotometry, the kinetics of the release of liposome contents at a temperature corresponding to the collapse of the microgel was investigated.

P 08

SYNTHESIS OF ANTI-TUBERCULOSIS DRUGS ENCAPSULATED FORMS

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Nanoscale polymeric carriers are of interest as components of medical systems, allowing to realize the direct transport of biologically active substances (BAS), prolong their action, prevent side spending, reduce toxicity. Their use is promising in many cases, including in the treatment of diseases associated with genetically determined disorders, oncological diseases, in the treatment of tuberculosis and a number of other diseases.

The most well-studied among nanoscale carriers are liposomes capable of delivering BAS into cells by various mechanisms, in particular, due to fusion of liposomes with cell membranes, which is accompanied by ingress of BAS into the cytoplasm, by adsorbing liposomes on the cell surface, finally, by endocytosis of various types when the liposome enters the primary endosome of the cell.

The aim of the work is to study the process of incorporation anti-tuberculosis substance by the example of protionamide into the aggregates based on amphiphilic poly-N-vinylpyrrolidone derivatives with one terminal thiooctadecyl groups with different molecular weights from 1 to 12 kDa, as well as identifying features of this process.

Nanoscale particles were obtained by three different methods, namely suspension, emulsion, dialysis.

Suspension method – preparation of nanoparticles using an ultrasonic excitation without subsequent removal of the organic solvent. The organic solvent is compatible with water.

Emulsion method – self-organization of micelles at the interface between phases using an ultrasonic excitation with following removal of the organic solvent. The organic solution is incompatible with water

Dialysis method – preparation of nanoparticles by free micelle formation without the use of ultrasonic dispersion

As a result of the experiments, it was established that the average hydrodynamic diameter of the particles obtained by the suspension method was 50 nm, and by emulsion was 100 nm. The particles obtained by the dialysis method have an intermediate size of 77 nm.

The amount of incorporated protionamide does not strongly depend on the molecular weight of the polymers and ranges from 90% to 98%, regardless of the particles obtaining method.

P09

SYNTHESIS OF SMART HYDROGELS BASED ON COPOLYMER OF ALLYL GLYCIDYL ETHER AND N-VINYL PYRROLIDONE MODIFIED WITH DOPAMINE

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A copolymer of allyl glycidyl ether and N-vinylpyrrolidone was obtained by radical copolymerization, its composition was studied, the molecular weight and the second virial coefficient in aqueous solution were determined. The modification of the synthesized copolymer with dopamine was accompanied by the opening of the epoxy cycle. The kinetics of the reaction was investigated, a mathematical description was given and the corresponding kinetic parameters were determined. The resulting product can form gels in the presence of ferric salts, as well as when treated with oxidizing agents. After oxidative crosslinking, a hydrogel is formed, which is not sensitive to the variation of the pH medium, as well as the presence of ligands. During crosslinking with iron salts, the hydrogel was sensitive to variations in the pH of the medium, as well as to the presence of ligands that form strong complexes with Fe^{3+} ions. The potential biocompatibility of the synthesized hydrogels is shown, as well as the possibility of their reversible destruction. The proposed approach can be useful in the development of new biomaterials, including those exhibiting high biocompatibility and bioadhesive. The work was supported by Mendeleev University of Chemical Technology of Russia. Project Number 006.

P10

POLYMERIC METAL COMPLEXES

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To date, described a large number of polymeric biologically active compounds of various chemical structures, containing various biogenic metals.The introduction into the polymer carrier of various atoms of biogenic metals, first of all transitional groups, and their biological activity are clearly not studied.This work is devoted to the development of amphiphilic polymers N-vinylpyrrolidone, containing side functional groups capable of forming nanoscale aggregates and prone to complexation with transition metals. Amphiphilic poly-N-vinylpyrrolidone was chosen as the basis of the used polymer carriers. As it is known, this polymer is the most widely used water-soluble synthetic polymer in drug systems. For the introduction of metal atoms into the polymer, the complexation method was used. In this case, groups capable of complexation were introduced into the side groups of the polymers. As such groups, amino acid residues (glycine, β-alanine and γ-aminobutyric acid) were used. The introduction of metal atoms into the polymer through its coordination complexation with amino acid groups made it possible to produce systems with reduced toxicity, in contrast to fairly toxic metal complexes with polymers (for example, poly-N-vinylpyrrolidone), in which the metal was bound to the polymer due to the hydrogen bond intermolecular interaction forces. Based on the synthesized polymers with side groups, poly-N-vinylpyrrolidone metal complexes with Co (II) and Mn (II) salts were obtained. The dependences of the instability constant on the pH of the solution are determined. From the data obtained, it was concluded that the best complexing agent is an amphiphilic polymer modified with glycine.

P 11

POLY(VINYL ALCOHOL) + BACTERIAL NANOCELLULOSE + AG COMPOSITE CRYOGELS

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Poly(vinyl alcohol) (PVA) cryogels are the macroporous physical gels of crystallization type formed as a result of cryogenic processing (freezing, incubation in a frozen state and thawing) of concentrated polymer solutions. PVA cryogels are widely used in various areas that include biomedical and biotechnological materials, strengthening of the thawed grounds, restoration of paintings and so forth.

In the present study, the wound dressing prototypes based on PVA cryogels have been elaborated. In order to increase the mechanical rigidity of such gel materials the small particles of bacterial nanocellulose (BNC) were incorporated into the gel system. In addition, to impart the antibacterial properties to such composite cryogels, a so-called "nano-silver" was entrapped into the gel matrix. These Ag-bearing species were as follows: (i) the colloidal silver nanoparticles (Ag-bion) were incorporated during the formation of the cryogel; (ii) silver nanocrystals were formed directly inside the PVA/BNC-cryogel. The antibacterial activity of the materials thus formed have been examined with respect of Escherichia coli DH5α cells as the model Gram-negative bacteria and Bacillus subtilis B-522 cells as the model Gram-positive bacteria.

The release of silver cations from the system showed that the concentration of the outgoing ions is proportional to the filler amount in the composite. Re-sorption kinetics of Ag ions was studied by the conductomety method.

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P 12

TOXICITY OF SILVER NANOPARTICLES IN 4T1 AND A2780 CELL LINES.

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Nanoparticles (NPs) are defined as particles having all dimensions less than 100 nm. The small size of NPs results in unusual chemical and physical properties different from a bulk material. NPs have many applications in biology and medicine, as antibacterials, therapeutics, transfection vectors, fluorescent labels etc. One of the most generally used NPs are silver nanoparticles (AgNPs). First of all, they have strong antimicrobial activity and are widely used in various medical and general applications, among others, in cosmetics, odor resistant textiles and underwear. Though AgNPs belong to the most frequently investigated NPs, there is still a serious lack of information about the toxicity of AgNPs to humans, in particular the differences between the action of particulate and ionic silver.

The aim of this study was to compare cytotoxicity and genotoxicity of AgNPs in two cell lines: A2780 and 4T1. Both cell lines are widely used as a model cells of human ovarian carcinoma and murine mammary carcinoma, respectively. The cells were exposed to AgNPs coated with citrate (AgNPs(cit) or PEG (AgNPs(PEG), or $AgNO_3$ in concentration range of 1.17-300 µg/mL for 24, 48 (4T1 cells) or 0.5- 150 µg/mL for 24h (A2780), and thereafter the cytotoxic effect of AgNPs was measured by the resazurin assay. $AgNO_3$ was more toxic than AgNPs for both cell lines, while AgNPs(PEG) were less toxic than AgNPs(cit). When comparing two cell lines 4T1 cells revealed to be less sensitive to silver than A2780 cells.

On the basis of toxicity studies we determined IC_{90} and IC_{50} concentrations that reduce metabolic activity for 10% and 50%, respectively. These concentrations were used to study ROS generation and genotoxicity. Oxidation of H_2DCF-DA was measured as a general indication of generation of ROS production. The ROS production intensity reflect a general pattern observed for cytotoxicity, i.e. $AgNO_3$ > AgNPs(cit) > AgNPs(PEG). The A2780 cells showed 30% higher levels of ROS after treatment with AgNPs compared to 4T1.

Similarities were also observed in induction of oxidative damage to DNA. $AgNO_3$ was the most genotoxic agent followed by AgNPs(cit) and AgNPs(PEG). Interestingly, when formation of oxidative damage to the DNA was compared between the cell lines, it did not follow neither cytotoxicity pattern nor the pattern of ROS production. Comet assay analysis revealed more damage in 4T1 cells than A2780.

In conclusion, whereas a simple comparison of different NPs in one particular cell line gave similar results in three endpoints tested, the comparison between cell lines revealed additional factors, e.g. capability to repair damage to DNA or differences in cellular signaling, that might affect cellular response to nanoparticles.

P 13

OXIDATIVE POLYMERIZATION IN THE SYNTHESIS OF BIOCOMPATIBLE MATERIALS

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Poly-conjugated systems have a complex of unique properties, such as the presence of electrical conductivity, activity in redox reactions, and in some cases they are characterized by high heat resistance, weatherability, and biocompatibility. At the same time, the mechanisms of the processes underlying the synthesis of polymers with a developed system of conjugated bonds remain the subject of discussion. In particular, there is no final clarity in the mechanism of oxidative polymerization of aromatic amines and pyrroles. Products of oxidative polymerization of aromatic amines and pyrroles in some cases exhibit high biocompatibility and varying the side substitutes allows fine-tuning the properties of these polymers. Therefore, some derivatives of polyaniline and polypyrrole can be used in the manufacture of biosensors, materials for hemosorption, carriers of nucleic acids and materials with high hemocompatibility. Visible prospects are opening when polypyrrole and polaniline are used as carriers of pharmacologically active substances and plant growth regulators.

At the same time, the use of polyconjugated systems is limited by the substantial difficulties of their processing into target products, since they are not capable of passing into a viscous state and are soluble only in certain bipolar aprotic solvents. At the same time, polypyrrole has no solubility in any of the known solvents, as it is a crosslinked polymer. Therefore, for the application of polyconjugated systems, it is necessary to obtain their stable dispersions or deposition them on the surfaces of solid carriers. In this report, special attention is paid to the consideration of the kinetic regularities, properties and applications of oxidative polymerization products, which form in the presence of stabilizers or carriers. An explanation of the auto-acceleration effect is given, the mechanism of oxidative polymerization is proposed, and quantitative models are constructed describing the kinetics of this class of reactions and the molecular-mass distribution of the resulting products are found. The work was supported by Mendeleev University of Chemical Technology of Russia. Project Number 006.

P 14

MAGNESIUM SULFATE AMELIORATES CARBON MONOXIDE-INDUCED CEREBRAL INJURY IN MALE RATS.

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Carbon monoxide (CO) has been shown to induce several cardiovascular abnormalities, as well as necrosis, apoptosis and oxidative stress in the brain. Magnesium sulfate (MS) has been shown to have beneficial activities against hypoxia in the brain. In the present study, the possible protective effects of MS against CO-induced cerebral ischemia were investigated. For this purpose, 25 male Wistar rats were exposed to 3,000 ppm CO for 1 h. The animals were divided into 5 groups (n=5 in each group) as follows: The negative control group (not exposed to CO), the positive control group (CO exposed and treated with normal saline), and 3 groups of CO-exposed rats treated with MS (75, 150 and 300 mg/kg/day) administered intraperitoneally for 5 consecutive days. On the 5th day, the animals were sacrificed and the brains were harvested for the evaluation of necrosis, apoptosis and oxidative stress. Histopathological evaluation revealed that MS reduced the number and intensity of necrotic insults. The Bax/Bcl2 ratio and malondialdehyde (MDA) levels were significantly decreased in a dose-dependent manner in the MS-treated rats compared to the positive control group, while a significant dose-dependent increase in Akt expression, a pro-survival protein, was observed. In addition, MS administration reduced pro-apoptotic indice levels, ameliorated histological insults, favorably modulated oxidative status and increased Akt expression levels, indicating a possible neuroprotective effect in the case of CO poisoning. On the whole, the findings of this study indicate that MS may prove to be useful in protecting against CO-induced cerebral injury.

P 15

ACCUMULATION OF CATIONIC FOLATE-ASSOCIATED LIPOSOMES IN CELL LINES WITH DIFFERENT FOLATE RECEPTORS EXPRESSIONS

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In order to minimize the negative side effects of anticancer therapy, specific targeted nanocarriers can be used. Cationic liposomes are widely used due to their biocompatibility and ability to effectively encapsulate both lipophilic and hydrophilic compounds, as well as genetic material. Since many tumor cells are characterized by folate receptors (FR) overexpression, to provide targeted drug delivery cationic liposomes could be modified with folic acid.

The aim of this work was to study the accumulation efficiency of cationic folate-associated liposomes (FLPs) in cell lines which are known to differ in FR expression levels. Recently, the doxorubicin-loaded FLPs with mean diameter of 135±5 nm and ζ-potential of +51 mV were obtained by new post-modification technique. In the current study the FLPs accumulation efficiency was evaluated in vitro using flow cytometry in a number of cell lines (rat brain glioma C6 cells, human brain glioma U-87MG cells, human breast adenocarcinoma MCF-7 cells, human mesenchymal stem cells MSC) which differ in FR-expression. To block an endocytosis, the experiment was carried out at physiological temperature (37°C) and at 4°C. Thus the cellular uptake of FLPs at 4°C could proceed only by means of a receptor-mediated endocytosis. Common liposomes without ligands (LPs) were used as a control. Accumulation efficiency was similar in all cell lines at 37°C, while at 4°C LPs uptake by cells was not observed at all. The FLPs accumulation levels were found to be higher in C6 and MCF-7 cells (with high FR-expression) compared to those in MSC and U-87MG cells (with low FR-expression) both at 37°C and 4°C. However, FLPs accumulation at 4°C was lower than at 37°C.

This study was supported by Russian Foundation for Basic Research (grant 18-34-00919 in part of cerasomes, grants 17-54-33027 and 18-04-01087 in part of 3D tumor spheroids).

P 16

HYBRID CATIONIC POLYMERS COMPOSED OF ARGININE AND SPERMINE – SYNTHESIS AND PRELIMINARY IN VITRO CYTOTOXICITY STUDY

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Polymeric systems bearing positive charges or synthesized in the presence of novel cationic entities, incorporated on their backbone and/or as side chains, are considered as cationic polymers (CPs). These systems exhibit unique physical-chemical properties, and their ability that allows further modification, renders them appealing for numerous applications. Interest in CPs results from their potential to form polyelectrolyte complexes with nucleic acids (DNA, and RNA). In addition their inherent bioactive properties such as antimicrobial, stimuli responsiveness, antioxidant, antitumor and anti-inflammatory make CPs more promising for further enhanced therapeutic potential. CPs are also suitable precursors for constructing smart hydrogels which are of interest for biomedical applications as controlled (e.g. pH dependent) drug eluting systems, etc.

Proceeding with a systematic study of new biodegradable CPs we have synthesized new "hybrid" CPs (HCPs) by combining the "parent" homo-polymers containing either arginine (R) [1] or spermine (Spm) [2] residues in the backbones, for the following reasons:

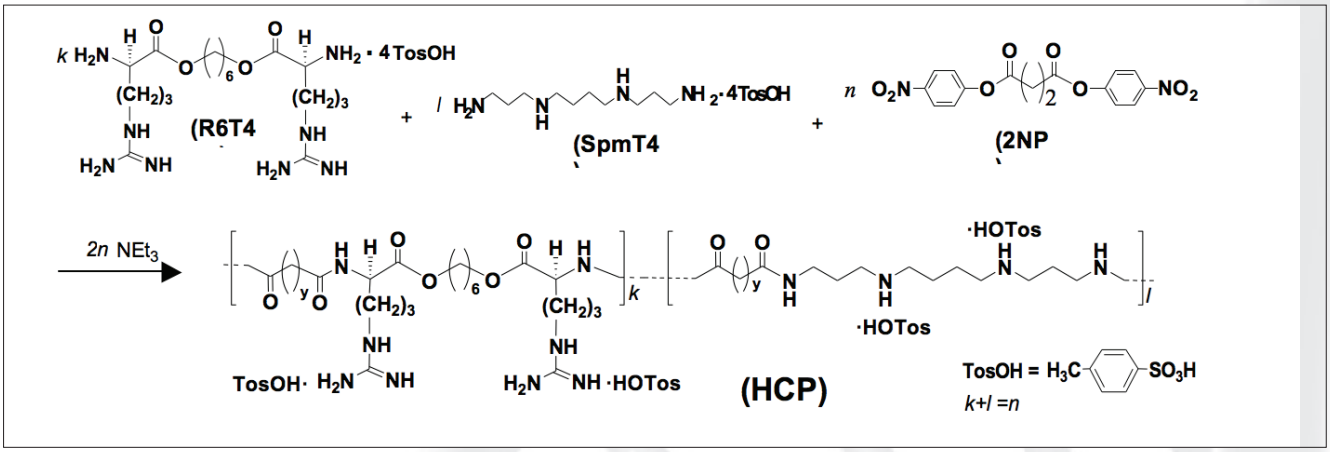
To increase cell compatibility of the Spm-based CPs (comes from R-based parent);

To increase transfection activity of the R-based CPs (comes from Spm-based parent);

To facilitate the synthesis of non-cross-linked/soluble CPs on the basis of polyamines;

To obtain new CPs suitable as precursors of biodegradable hydrogels promising for both biomedical (e.g. as drug eluting smart gels) and technical (e.g. in batteries) applications.

The HCPs were synthesized by solution polycondensation of bis-nucleophilic comonomers such as R6T4 and SpmT4 with bis-electrophilic monomer - di-p-nitrophenyl succinate (2NP), as depicted below:



The ***in vitro*** cell compatibility study of the obtained HCPs confirmed our assumption – the higher is R content in the HCP the higher is its cell compatibility and vice versa.

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P 17

THE STUDY OF MOLECULAR MASS CHARACTERISTICS AND MICELLE FORMATION IN A SOLUTION OF AMPHIPHILIC OLIGOMERS USED TO INCAPSULATION OF DRUGS.

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End-capped amphiphilic polyvinylpyrrolidone and surface-active oligomers obtained by hydrolytic polycondensation of adducts on the double bond of 2-cyanoacrylic acid esters are used as nanoscale carriers of drugs and genes. Their effectiveness is crucially dependent on the size of self-assembled capsules and on the molecular weight of the oligomers forming the wall.

Measurement of molecular mass characteristics of surface-active polymers and oligomers, forming associates in solutions, remains an intractable scientific and practical task. This study proposes a method for determining molecular mass characteristics and sizes of associates of surface-active oligomers in organic solvents using a combination of three physicochemical methods: dynamic light-scattering, static multi-angle light-scattering, gel-penetrating chromatography with double detection, refractometric and matrix UV detectors.

Of all the studied methods for determining the molecular mass characteristics and sizes of micelles, the method of end groups of NMR and GPC in an organic solvent is suitable for measuring molecular weight. Static light scattering is not suitable for determining molecular masses and gives highly overestimated results. The investigated polymers form two types of micelles in solution (single-layer and two-layer); however, in the case of the encapsulation of hydrophobic substances, only single-layer micelles are formed.

P 18

MATRIX COPOLYMERIZATION OF ANILINE AND 2-AMINOPHENETHYL ALCOHOL USING A LACCASE-MEDIATOR SYSTEM

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A one-step synthesis of a conducting copolymer of aniline and 2-aminophenethyl alcohol has been performed on a poly (2-acrylamido-2-methylpropanesulfonic acid) matrix (PAMPS). Highly redox-potential laccase from the fungus Trametes hirsuta was served as a catalyst for polymerization and hydroxybenzotriazole (HBT) was used as a mediator. As a result the conductive copolymer was obtained, the primary alcohol groups of which were oxidized to aldehyde groups. The formation of carbonyl groups in the copolymer chain was confirmed by a silver mirror test and FTIR studies. Peaks at 1740 and 1207-1220 cm-1 were observed on the FTIR spectrum of the copolymer, which can be attributed to tensile and deformation vibrations of the carbonyl group.

For the modification of the copolymer laccase substrate L-dioxyphenylalanine (DOPA) was used. Since the optimum pH of ***T. hirsuta*** laccase activity is 4.5 and Schiff bases are unstable in acidic medium the forming copolymer/DOPA conjugate was reduced with sodium borohydride. As a result of laccase-catalyzed oxidation of DOPA the product with an absorption maximum in the 570 nm area was formed in the conjugate.

Thus, the possibility of using the laccase-mediator system for the synthesis of the conducting copolymer of aniline and 2-aminophenethyl alcohol with reactive aldehyde groups was demonstrated. The formation of aldehyde groups in the copolymer chain allows further modification of the resulting product in order to obtain conducting composites that can be useful for biosensor devices, neural interfaces, etc.

P 19

HUMIC ACIDS AND SILVER NANOPARTICLES AS ANTIMICROBIAL ADDITIVES

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The organic part of peat consisting of humic acids (HA) represents natural high molecular weight substances with complicated structure. HA macromolecules contain numerous polysaccharides, peptides, amino acids, sterols, fatty acids, polyphenols and other compounds which provide their high biological activity. HA have antioxidant, anti-inflammatory properties, show antiviral and antibacterial activity, can solve as detoxicants and hepatoprotectors, have a positive effect on the human immune system, and moreover, possess antiallergic and anti-sclerotic effects. All these complex properties allow considering them as perspective base for a wide application as active ingredients for pharmaceuticals, cosmetics and dietary supplements.

In this study soluble forms of HA salts of Na^+, K^+, NH_4^+ were obtained by the peat treatment of an aqueous solution of appropriate bases at elevated temperature.

We have done a comparative analysis of antimicrobial activity in model therapeutic mud compositions containing silver nanoparticles as antimicrobial agent. HA were used as recovery agents for silver nanoparticles at sole systems. It was also identified that silver nanoparticles may form directly during the process of peat hydrolysis with $AgNO_3$ salts.

For comparison of antimicrobial effects, the standard preservative Germaben-2 (0.1% mass.) and nanoparticles (0.012% mass.) were used with therapeutic mud compositions which were prepared by hydrolysis of concentrated peat suspensions under 0,1M NaOH at 60°C. The total amount of mesophilic aerobic and facultative anaerobic microorganisms (QMAFAnM) and filamentous fungi in the compositions was determined.

Thus, investigations have shown that silver nanoparticles in 0.012% mass. have high antimicrobial activity and can be used as a qualitative antimicrobial additive at therapeutic mud compositions production based on humic acid substances.

P 20

DEVELOPMENT OF A METHODOLOGY FOR ANALYSIS OF LIQUID SOAP ANTIMICROBIAL ACTION

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The study focuses on the development of methods and the selection of criteria for evaluating the antimicrobial activity of certain types of cosmetic products. The antimicrobial activity of samples of liquid soap with antimicrobial additives (triclosan as the most common antimicrobial component, the essential oil of tea tree from the list of natural components and undecylenamidopropyltrimonium methosulfate as an alternative to previous antimicrobial agents) was investigated. Evaluation of the antimicrobial activity of the prepared samples of liquid soap was carried out in relation to natural microflora of hands using the wash method and in relation to sanitary-indicative microorganisms by the disk-diffusion method according to the size of the lack of growth zone on agar medium of test-organisms (Staphylococcus aureus FDA 209P, Essherichia coli ATCC 25922, Candida albicans ATCC 885-653, Bacillus subtilis VKPM – B-13183, Pseudomonas aeruginosa VKPM – B-8243).

Studies have provided evidence that samples of liquid soap with such antimicrobial additives as tea tree oil, triclosan, undecylenamidopropyltrimonium methosulfate showed antimicrobial activity against the natural microflora of the hands. In the maximum allowable concentration, the degree of cleaning of the hand surface was: 85% for tea tree oil, 98% for triclosan and 74% for undecylenamidopropyltrimonium methosulfate. While in the control sample (liquid soap without the addition of antimicrobial additives), the degree of cleaning the surface of the hands was 52%.

At the same time, in relation to sanitary-indicative microorganisms, the selective effect of the studied samples was found. It was found that all of the studied samples show antimicrobial activity against ***St. aureus*** and ***B. subtilis*** and was not detected activity against ***P. aeruginosa***. Antimicrobial activity towards ***E. coli***, was found only for soap containing tea tree oil. And the activity against the ***C. albicans*** yeast was only observed for soap with undecylenamidopropyl trimonium metosulfate.

P 21

CATALYSIS OF AROMATIC AMINES OXIDATIVE POLYMERIZATION WITH METHYLENE BLUE

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The kinetics of aniline and pyrrole oxidative polymerization was studied in the presence of methylene blue dye that simulates quinone diimine fragments of polyaniline. Earlier, the authors developed theoretical ideas according to which the autocatalytic course of aromatic amines and pyrroles oxidative polymerization is associated with the formation of a complex with charge transfer between the monomer and electron-deficient segments of the oligomers chains and polymers formed. Although this hypothesis is supported by a number of kinetic studies, the direct determination of the such complexes structure with charge transfer presents known difficulties. Therefore, the search for adequate low molecular weight models is of particular interest.

The reduction of aniline oxidative polymerization induction period is shown when methylene blue is introduced into the reaction system, what simulates the oxidized fragments of the polyaniline chain. A quantitative analysis of the aniline oxidative polymerization kinetic laws in the presence of methylene blue has been carried out. Methylene blue has been shown to be an effective oxidative polymerization catalyst. A significant acceleration of the oxidative polymerization of pyrrole was also found with the introduction of catalytic amounts of methylene blue into the reaction system.

Confirmation of charge transfer complex formation between aniline and methylene blue was obtained, which is a powerful argument in favor of a mechanism explaining the autocatalytic course of the aniline oxidative polymerization to form charge transfer complexes in the adsorption layer.

Assumptions have been made about the possible uses of oxidative polymerization catalysis with methylene blue in the development of new efficient approaches in obtaining biocompatible coatings on the surfaces of various carriers. The work was supported by Mendeleev University of Chemical Technology of Russia. Project Number 006.

P22

SOLID PHASE SYNTHESIS OF CALCIUM STEARATE ON MODIFIED SCREW EQUIPMENT

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For the first time, the technology of solid-phase synthesis of calcium stearate was developed under conditions of low-temperature (up to 100 ° C) and mechanical force action associated with the application and subsequent relaxation of the stress field on the reaction mixture of the trimolecular reaction of stearic acid and calcium hydroxide. Under the conditions of mechano-energetic impact in a modified screw apparatus, providing effects on the reaction mixture of continuous plastic deformations, various kinds of defects are formed on the surface of the molecules of the reactants, expressed in the anisotropy of the crystal lattice. Hydrogen bonds arising in carboxylic acids are among the strongest among other hydrogen bonds; their energy is 29 kJ / mol. At the same time, the electron density is shifted towards the most electron-withdrawing oxygen atom of the carbonyl group. Mechano-energetic effect leads to a weakening of the bond between oxygen and hydrogen in the hydroxyl group and ease of cleavage of the hydrogen atom from the hydroxyl in the form of a proton (H +), which is expressed by mass transfer at the interface between the heterogeneous heterophase reaction.

The use of an extrusion apparatus with one or more satellite augers provides, firstly, the maximum degree of dispersion of the components of the reaction mixture, and secondly, an unprecedentedly large area of the interface between the reagents and the topochemical reaction.

The time of product synthesis during the liquid-phase process is reduced, in the case of the non-catalytic process, from several hours to 2.28-10 minutes, depending on the configuration of the extrusion equipment. The samples obtained by the solid-phase method were characterized by a high efficiency of the stabilizing action and corresponded to the standards of industrially manufactured products.

Such conditions, recreated in the laboratory installation of a screw apparatus, provide for intensification of the technological process, energy-saving and environmental safety.

The influence of mechanical energy effects: pressure and plastic deformation on the process of solid-phase synthesis of calcium stearate inside the extruder cavity was shown.

P 23

ANTI-ADHESIVE MATERIAL BASED ON HYDROPHOBIC CHITOSAN NANOPARTICLES

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The formation of adhesions is a frequent complication of surgical interventions on the abdominal organs and small pelvis. The development of anti-adhesive barrier materials is an urgent biomedical challenge. The purpose of this study is to analyze the anti-adhesion effect of nanoparticles (NPs) obtained based on a hydrophobized succinoylchitosan (SC). To increase adhesion to mucous membranes, SC 200 kDa derivatives modified with ethanoic, butanoic, hexanoic and lauric acids with different degrees of substitution were obtained. Of all the derivatives were obtained NPs method of calcium precipitation. NP was isolated by centrifugation; size and charge were analyzed by dynamic light scattering. The size and yield of the NPs depended on the degree of substitution and the length of the hydrophobic residue. From the obtained derivatives, hexanoyl-SC (HSC) possessed optimal properties, forming stable NP with a size of 200-300 nm. For visualization of cell binding in vitro and analysis of NP biodistribution in vivo, the amino derivative of the BDP FL dye was used, which was included in the NP when they were formed. It has been shown that NPs effectively bind to MDCK cells and are recorded in cells for at least a week. The analysis of anti-adhesions was carried out in a model of adhesions in C57BL/6 mice, for which mice were operated on under anesthesia and the upper layer of the cecum and the adjacent abdominal wall was damaged. NP applied to damaged tissue. Mice were dissected after 1 week to assess the level of adhesion formation and biodistribution of the NP. The cells of peritoneal exudate, fragments of the caecum and abdominal wall, liver, spleen and lymph nodes of Peyer's patches were taken. It was shown that the low-frequency choke-sticks significantly reduced the formation of adhesions (from 4 to 1 level compared to the control). BDP biodistribution analysis showed binding of NPs to macrophages and neutrophils of peritoneal exudate; cells of damaged tissues, slight accumulation in the liver and spleen, the minimum number in the lymph nodes. Thus, the introduction of NP HSC reduces the formation of adhesions and can be used during operations on the abdominal cavity.

P 24

HYDROGEL MATRIX CONTAINING POLYVINYLPYRROLIDONE, POLYELECTROLYTE AND CELLULOSE DERIVATIVES AS CARRIER FOR MEDICAL APPLICATIONS

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Today the introduction of therapeutic and prophylactic drugs containing enzymes with multi-aspect action in medical practice is obviously the relevant and important task. This also applies to highly purified proteinases belonging to the group of hydrolases used in systemic enzyme preparations, which meet a long exposure time requirement. Proteolytic enzymes are biological antiseptics and have an antitoxic, anti-inflammatory, necrolytic effect. The mechanism of the action of proteolytic enzymes on an infected wound is the hydrolysis of toxic microbial metabolites of a protein nature, which contributes to the earlier granulation occurrence and causes the epithelization acceleration.

In this investigation the effect of ionizing radiation on a hydrogel matrix consisting of polyvinylpyrrolidone, polyelectrolyte (sodium alginate), cellulose derivative (hydroxyethylcellulose) and containing terrilytin, as a proteolytic enzyme, was determined in order to consider such system as a proper carrier for biomedical application. The main process characteristics affecting the final activity of the introduced drug were studied.

In the presence of sodium alginate, the relative proteolytic activity is much higher, since the introduction of polyelectrolyte into the system leads to an increase in the stabilization of the enzyme, which is correlated with the previously obtained data on the calculation of the equilibrium swelling coefficient. In addition, in polymeric hydrogels, complexation of terrilytin with sodium alginate occurs as a result of the recharging of part of the protein groups. It is possible due to the electrostatic field of the ionic matrix, as well as due to the formation of additional hydrogen bonds. Proteolytic activity in such systems is maintained at a high level before and after irradiation. The optimal dose range for these systems was 20 ± 5 kGy. The dose of absorbed radiation is one of the main parameters determining the number of intermolecular crosslinks per one polymer molecule. Further, the results of the present study will allow developing a final drugs form with optimized properties and characteristics.

P 25

PH-SENSITIVE MULTI-LIPOSOMAL NANOCONTAINERS BASED ON CHITOSAN

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The application of liposomes as nanocontainers for the delivery of biological active substances was suggested decades ago. In order to cause the liposomes to open and release the encapsulated drug in a special area, they are modified with a substance (a switch) capable, under the action of an external stimulus, to disorder the lipid bilayer, thus inducing a release of the encapsulated drug from the liposomes to a surrounding solution. Among the other stimuli, pH and temperature are of particular interest since in pathological areas these parameters often differ from the normal. Despite quite a wide choice of pH-sensitive liposomes, there is still a considerable challenge to synthesize liposomes which quickly respond to small variations of pH and release most of the encapsulated drug in a short time. Multi-liposome assembly, for example via immobilization of several liposomes on a nano-sized colloid particle, can increase the efficacy of liposome interaction with cells and therapeutic effect of a liposomal drug.

In this work we describe liposomes, composed of conventional zwitter-ionic egg yolk lecithin (EL), which additionally contained a derivative of lithocholic acid with anionic and cationic groups attached to the opposite ends of the steroid core. This ampholytic switch (AMS) changed its orientation in the liposomal membrane thus adapting to acidity/basicity of the outer solution. The rotation of AMS induced disordering of the membrane and the immediate cargo release. The pH-sensitive liposomes were characterized by a low cytotoxicity, have potential applications in the drug delivery field. In order to increase the efficiency of delivery, liposomes were concentrated by immobilizing on the surface of cationic chitosan nanoparticles. Each chitosan particle could adsorb up to 100 anionic liposomes. The conjugates demonstrated stability towards dissociation in physiological media. The obtained pH-sensitive multi-liposomal nanocontainers have potential applications in the drug delivery field.

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P 26

KINETICS AND MECHANISM OF INTERACTION OF POLYVINYL ALCOHOL WITH EPICHLOROHYDRIN IN AN ALKALINE MEDIUM

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The combination of high biocompatibility and sufficient strength in the swollen condition has provided for a wider application of polyvinyl alcohol hydrogels in biomedical areas. One of the classical methods for the synthesis of polyvinyl alcohol hydrogels is the treatment of its aqueous solution with epichlorohydrin in an alkaline medium. Although this reaction is widely discussed in the literature, to date, the kinetic patterns of its occurrence have not been established.

In this work, analysis of the kinetic patterns of the interaction of polyvinyl alcohol with epichlorohydrin in an alkaline medium, taking into account the side processes of hydrolysis of the initial epichlorohydrin, as well as the intermediate epoxy-containing compounds was conducted. It is shown that the total concentration of epoxy groups in the system decreases with time, while the concentration of immobilized epoxy groups associated with the chain of polyvinyl alcohol passes through a maximum. The change in molecular mass distribution during modification of polyvinyl alcohol with epichlorohydrin is shown and a quantitative model for changing the branching density over time is proposed. Polyvinyl alcohol branching products, the formation of which precedes the formation of a three-dimensional network, have been extracted, and their properties and some aspects of biocompatibility have been investigated. The change in the mechanical properties of films of branched polyvinyl alcohol in the process of its formation was investigated. High hemocompatibility of branching products of polyvinyl alcohol by epichlorohydrin was detected. The work was supported by Mendeleev University of Chemical Technology of Russia. Project Number 006.

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P 27

DESTRUCTION OF SOLID ELEMENTS OF A MULTIPHASE COMPOSITION IN THE INTERSTRUCTURE SPACE OF THE EXTRUDER

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The work is devoted to the study of viscous fluid flow in a flat section of the interturn space of a planetary roller extruder. Mathematical modeling of the flow is presented. A simplification of the model is used, in which the flow region is represented as a square cavity with three moving and one fixed walls. The problem is solved numerically using the control volume method using the open integrated platform OPENFOAM. Nonphysicality in places of discontinuity of derivatives is eliminated by smoothing. The distributions of the difference between the principal stresses and the velocity field inside the flow region are calculated. Abnormally high values of pressures and stresses were found in the regions adjacent to the junction points of the boundary surfaces, the singularity regions. Discusses the possibilities of stress on the structure of the fluid. As a result of a numerical study of the flow in the inter-turn space, we can predict the following possible mechanism of the process of destruction of solid inclusions in a liquid flow:

- solid inclusions and fibers after passing through the inter-turn space can disintegrate as a result of exposure to internal stresses;

- solid inclusions and fibers falling in the region of singularity, are significantly affected by internal stresses, which can lead to their grinding;

- a significant pressure gradient squeezes the crushed particles into the central part of the flow area, which ensures that new portions of the original solid inclusions fall into the singularity range.

P 28

WATER-IN-OIL MICROEMULSIONS BASED ON NONIONIC SURFACTANTS AS TRANSDERMAL DELIVERY SYSTEMS

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Some of cosmetic and pharmaceutical products are based on water-in-oil microemulsion systems. The use of such compositions for transdermal delivery of drugs and biological active ingredients has several advantages, like thermodynamic stability, affinity to skin lipids, nanosized droplets, large volume of solubilized substances.

This research was aimed to characterize microemulsion systems based on nonionic surfactants (PEG-8 or PEG-6 caprylic/capric glycerides, polyglyceryl-6-dioleate, PEG **sorbitan monolaurate**) by different experimental techniques.

The viscometry, conductometry, temperature and acoustic spectroscopy methods were used for determination of the phase transitions in microemulsions depending on the water/oil phase ratio, polarity of oil phase, the content and the type of electrolyte used. The results from conductivity and viscosity studies suggested a percolation transition such as water-in-oil/percolating cluster/bicontinuous microemulsions. The results from all techniques are in good agreement. Comparison of conductometric and viscometric data showed that structural changes occur in one concentration interval of water in the system. Thus, compositions with mole ratio of PEG-8 caprylic/capric glycerides – 0,8 registered structure transitions to percolation cluster at 0,23 mass water ratio and to bicontinuous system at 0,35. The studies revealed the percolation character of the specific conductivity of microemulsions at the electrolyte NaCl presence.

A pseudoternary phase diagram was constructed using water titration method. By the dynamic light scattering method was determined that droplet size of investigated microemulsions is not more than 100 nm.

The results obtained allow us to use such systems for further investigation as pharmaceutical and cosmetic compositions with controlled transport characteristics.

P29

ACTION OF POLYSACCHARIDE DRESSINGS MATERIAL CONTAINING ENZYMES FOR WOUND HEALING

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The development of new effective purulent wounds treatment remains one of the top priorities for research. Modern wound healing composition must have a number of necessary properties, listed below. It should absorb purulent discharge, have a cleansing, antioxidant and antimicrobial action. One of the main problems in the production of materials which containing various therapeutic agents is the loss of their biological activity during the preparation, drying, storage and use of medicines under the effect of human body temperature, wound pH, various inhibitors, etc.

The complexity of the production of such materials for the wounds care lies in the fact that the developer must ensure a long and controlled release of the active compound (therapeutic agent), while preserving the other properties of wound healing compositions. The biological activity of the developing products should be maximally realized in the wound. Since such biomaterials are disposable products with a short duration (usually about 24 hours but not more than 72 hours). It is necessary to know the mechanisms of their work and utilization in the body, when using immobilized preparations of various therapeutic agents in medical practice.

The study of the decay kinetics of the created therapeutic systems under model conditions, as well as the analysis of the compounds formed in this process, is one of the main stages in the development of wound healing coatings, which not only justify the safety of using the compositions, but also explain the principle of their work on the wound.

The decomposition of composites created by us begins immediately from the moment of its immersion in a liquid medium. The process of hydrolytic destruction and desorption of the therapeutic agent begins. The appending of chitosan into the created material slows down the processes of destruction occurring in a liquid medium.

The study of the antiradical properties of the carriers (unmodified cellulose, and dialdehyde cellulose of various degrees of oxidation) did not reveal a pronounced antioxidant activity of the materials. It can be concluded that there are no antioxidant properties of the cellulose matrix. It was also established that the products of hydrolytic degradation of compositions possess antioxidant activity.

The absence of toxic free aldehydes as products of cellulosic carrier's hydrolytic degradation was confirmed in an experiment to study the enzymatic activity and HPLC chromatography data.

It was concluded that the appending of chitosan affects not only the kinetics of the composition destruction, the kinetics of therapeutic agent's release, but also their biological properties.

P30

POLYMERIC NANOPARTICLES BASED ON AMPHYPHILIC DERIVATIVES OF N-VINYL-2-PYRROLIDONE CONJUGATED WITH ANTITUMOR CYTOKINE TRAIL DR5-B/V114C

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Cytokine TRAIL DR5-B conjugated with polymeric nanoparticles based on N-viny-2-pirrolidone by carboxyl groups on the polymer to aminogroups of the protein lose its antitumor activity, perhaps due to cross-linking with aminogroups of lysines on the surface of the protein molecules. In this work we obtained an amphiphilic polymer based on N-vinyl-2-pyrrolidone modified by maleimide at the hydrophilic end of the polymer chain for covalent conjugation with antitumor cytokine TRAIL DR5-B/V114C by the cysteine-maleimide bond. As TRAIL DR5-B/V114C contains cysteine residue on the N-end, this method provides conjugation strictly by the N-end of the protein, ensuring the correct orientation of protein molecules on the surface of the nanoparticle.

Amphiphilic homopolymer based on N-vinyl-2-pyrrolidone was synthesized in the presence of initiator of radical polymerization azobisisobutyronitrile and transmitter and a chain growth regulator stearic acid chloride. The maleimide group was attached by interaction of the synthesized homopolymer with potassium maleimide.

For optimization of conjugated protein quantity we obtained micellar particles consisting of a 1:1 mixture of unmodified polymers and modified by maleimide, with the addition of a hydrophobic nucleus made of protionamide for stabilization. The particles were obtained by emulsion method by ultrasound homogenization of protionamide solution in chloroform and amphiphilic polymer solution in water. TRAIL DR5-B/V114C protein was produced in ***E. coli*** cells and purified on the affinity sorbent Ni-NTA followed by cation-exchange sorbent SP Sepharose. The protein was conjugated by overnight incubation with nanoparticles in 150 mm NaCl solution, pH 7.5 at room temperature. The obtained nanoparticles were precipitated by centrifugation. The protein content was determined by Bradford assay. Polymer nanoparticles entrapped the protein from the solution, while the protein retained its solubility. The loading capacity was 30 μg of protein per 1 mg of particles. The average particle size was determined by dynamic light scattering.

Thus, we obtained micellar nanoparticles based on N-vinyl-2-pyrrolidone modified by maleimide and stabilized by hydrophobic core, conjugated with antitumor cytokine TRAIL DR5-B/V114C by the cysteine-maleimide bond.

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THE POLYELECTROLYTE MULTILAYER CAPSULES MODIFIED WITH NANODIAMONDS

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Many medicine preparations have a serious disadvantage - negative effect on healthy tissues. However, directed transportation of medicine in the form of capsules gives an opportunity to secure an encapsulated component from influence of environment, deliver active substance to the site of action, therefore decrease side-effects of the medication and reduce the dose injected into the body. Recently a lot of attention is paid to polyelectrolyte multilayer hollow capsules modified with nanoparticles, which were prepared by layer-by-layer (LbL) technique. Embedment of the nanoparticles within the microcapsules shell enable to be sensitive to external influences like microwave radiation for remote release of cargo. There are two possible mechanisms of the microwaves effects on the microcapsules: the first one is related to the thermal effect of microwave radiation, another way is that molecules start to oscillate, which results in change of their complex structure and, therefore, might effect on the permeability of the capsules shell [1].

The goal of the current study was to fabricate the polymeric multilayer capsules assembled by polyelectrolytes with additional modifications with nanodiamonds for triggering by microwave radiation. Calcium carbonate particles with a size of 2-4 μm were used as colloidal templates and two oppositely charged polyelectrolytes (sodium polystyrene sulfate (PSS) and polyallylamine hydrochloride (PAH)) were used to form the polymer shell. The nanodiamonds were embedded into the capsule shell by adsorption between the polyelectrolyte layers. The $CaCO_3$ cores were dissolved by EDTA treatment followed by the hollow capsules formation.

The results demonstrate successful formation of the polymer capsules with nanodiamonds included into the shell. The capsules with nanodiamonds were found to be sensitive to the microwave irradiation, which is open up the opportunity of their triggering.

[1] Timin A. et al., Inorganic/Organic Multilayer Capsule Composition for Improved Functionality and External Triggering, Advanced Materials Interfaces, 2016

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P 32

CONTROLLED RELEASE OF PROTEIN FROM MAGNETO LIPOSOMES VIA NANO-MAGNETO-MECHANICAL ACTUATION

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The most studied nanocarriers to deliver substances of protein nature are liposomes. Encapsulation of proteins in liposomes prolonged the circulation time, enhanced the therapeutic efficacy and reduced the toxic side effects. One of its significant drawback is the slow release or complete loss of the release of active molecules. To increase the membrane permeability magnetic liposomes were used. Magnetic nanoparticles (MNPs) act as a mediator between the magnetic field and the magnetoliposomes. In this work, we study a new approach to simplify and improve the release of the drug from liposomes, functionalized with MNPs of various shapes – "spheres" and "rods", under the action of low frequency alternating magnetic field (LF- AMF). The behavior of MNPs in liposomes, exposed to LF-AMF, is characterized by Brown relaxation. The aim of this work was to develop magnetoliposomes, conjugated with spherical- and rod-like MNPs on their surfaces, and to study the effect of LF-AFM on their permeability.

Liposomes were produced via thin film method followed with the covalent linking of the N-dopamine coated MNPs to the carboxyl group of the liposomal surface. The samples were analyzed by dynamic light scattering, Nanoparticle Tracking Analysis, transmission electron microscopy, ATR-FTIR and spectrophotometry. Microscopy and ATR-FTIR analysis showed the changes in the lipid membrane behavior under exposures to LF-AMF due to magneto-mechanical actuation of MNPs. The study of the release of the fluorescent label from magnetoliposomes under exposures to LF-AMF (110 Hz, 90 mT) showed an increase in membrane permeability of liposomes conjugated with both types of MNPs – "spherical" and "rod-like". Despite of the low amount of the liposomes, conjugated with MNPs, the possibility to release of high-molecular Bowman-Birk Inhibitor (BBI, 6-8 kDa) from the liposomes under LF-AMF exposures was shown. The effect depended not on the frequency, but on the strength of LF-AMF. The maximal effect of the exposure to MF was detected in the case of spherical MNPs and the release of BBI was two times higher in comparison to control. Thus, the study provides the possibility to use magnetoliposomes, loaded with macromolecules of protein nature, as the effective therapeutic agents with controlled release.

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P 33

EFFECT OF A LOW FRECUENCY MAGNETIC FIELD ON POLYELECTROLITE MICROCAPSULES MODIFIED BY MAGNETIC NANOPARTICLES

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Magnetically controlled drug formulations attract particular attention and represent one of the promising directions of targeted drug delivery technologies. Polyelectrolyte capsules modified by magnetic nanoparticles can accumulate in the desired area of the body under the influence of the applied magnetic field. Besides, the permeability of the capsules and cargo release can be controlled by the magnetic field. Application of low frequency non heating magnetic field for these purposes offer prospects of high penetration ability into tissues, high locality and safety, which makes this method suitable for ***in vivo*** use.

In this work, we study the influence of low frequency magnetic field (50 Hz) with different properties on the morphology, integrity and permeability of the Poly(allylamine hydrochloride)/Poly(styrene sulfonate) multilayer capsules modified by magnetite nanoparticles. The capsules were obtained by the method of electrostatic Layer-by-Layer adsorption on the surface of calcium carbonate core templates. The capsules characterized using scanning electron microscope Jeol JSM-7401F, transmission electron microscope Tecnai Osiris, confocal microscope Leica TCS SPE. To assess the effect of the magnetic field of the microcapsules they were irradiated during incubation in a fluorescent dye fluorescein isothiocyanate. We suppose that under the irradiation some defects in the polyelectrolyte shell may appear, which contribute to the penetration of the dye into the multilayer shell. The dye fluorescence intensity profiles were obtained in the microcapsules irradiated with a pulsed magnetic field with varying pulse duration (100-300 ms) and the pause between pulses (10-100 ms). From the analysis of the experimental data the most promising exposure parameters of the magnetic field was found.

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REMOTELY CONTROLLED RELEASE FROM MAGNETOLIPOSOMES UNDER LOW FREQUENCE MAGNETIC FIELD: VIZUALIZATION BY MEANS OF CONFOCAL MICROSCOPY

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Liposomes are widely used as delivery systems for various drugs and biomolecules. However, they often exhibit poor release of encapsulated molecules and low specificity of their delivery. Magnetic nanoparticles (MNPs) incorporated into liposomes can trigger drug release from liposomes under exposures to low frequency magnetic field (LF-MF) through magneto-mechanical actuation of lipid bilayers. The aim of this work was to fabricate doxorubicin loaded magnetoliposomes (MLip-DOX) incorporating hydrophobic Fe_3O_4 nanoparticles (mean diameter of 5-6 nm) in their membranes and study the influence of LF-MF on the release of drug.

Liposomes were prepared via the thin film method from MNPs, egg lecithin, DSPE-PEG(2000) and cholesterol and using active loading method to entrap DOX. The samples were analyzed by dynamic light scattering, nanoparticle tracking analysis, transmission electron microscopy, ATR-FTIR and spectrophotometry. Microscopy and ATR-FTIR analysis showed the changes in the lipid membrane behavior under exposures to LF-AMF due to magneto-mechanical actuation of MNPs. As was shown by ATR-FTIR, the LF-MF application caused "melting" of the MLip membrane. The release behavior of DOX has been studied ***in vitro*** as a function of different parameters, that is, field frequency, exposure time. Confocal and fluorescent microscopy showed that, under exposure of liposomes loaded with the dye and DOX to LF-MF free DOX accumulated around the cell nucleus (in 4T1 cells monolayer) and lipids were located in cytoplasm as aggregates, in the case of non-treated MLip-DOX there was not free DOX in cells. Cytotoxicity test showed the higher toxicity of MLip-DOX after exposures to LF-MF in comparison to control (non-treated MLip-DOX). ***E***xperiments using spheroids (4T1 and MCF-7 cell lines) also showed increase of rate of DOX accumulation in nucleus after exposure of MLip-DOX to LF-MF. Thus, the study provides the possibility to use magnetoliposomes, loaded with drug, as the effective therapeutic agents with controlled release. Moreover, the effects of the exposure to LF-MF on release from MLip, observed ***in vitro*** on cells monolayer**,** were reproduced on cells spheroids which are more close to ***in vivo*** models, and have the same mechanism.

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HYBRID MAGNETITE-GOLD NANOPARTICLES AS ALL-IN-ONE PLATFORM FOR THERANOSTICS

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High-quality, 25 nm octahedral-shaped Fe3O4 magnetite NPs are epitaxially grown on 9 nm Au seeds using a modified wet-chemical synthesis (Efremova et al, Scientific Reports, 2018). Subsequently, the hybrids are covered with a biocompatible DSPE-PEG-COOH polymeric shell (Efremova et al, Beilstein Journal of Nanotechnology, 2018). Then, Fe3O4-Au NPs are functionalized with covalently attached Sulfo-Cyanine5 NHS ester derivative (Cy5) fluorescent dye via thiol-Au bonds allowing NPs tracking. In addition, the Nile Red dye is loaded into the polymeric shell at the Fe3O4 surface as a model for a hydrophobic drug (e.g. paclitaxel). Further, functionalized Fe3O4-Au hybrids are thoroughly tested in 4T1 murine breast cancer model in vitro and in vivo.

First, Nile Red-loaded Cy5-labeled NPs (NRed-NP-Cy5) have been inoculated into 4T1 cell culture and monitored for 30 min by real-time confocal microscopy in vitro. Both Nile Red and Cy5, conjugated with NPs, are localized in cytoplasmic vesicles starting from 10 min after inoculation with maximum accumulation at 30 min. Some granules turn to be Nile Red-positive, but Cy5-negative, suggesting that these are the result of dye release from NRed-NP-Cy5 inside cells.

In vivo imaging of NRed-NP-Cy5 delivery and biodistribution was implemented using intravital microscopy in 4T1-GFP-bearing animals. Immediately after i.v. injection, both dyes are detected on NPs resulting in vasculature counterstaining. Real-time imaging reveals the Nile Red release in the tumor microenvironment. Within 2 min after NPs attachment to the vessel wall, Nile Red diffuses into the surrounding malignant tissue. 6 h after NRed-NP-Cy5 i.v. administration, the Cy5 signal is detected throughout the tumor. Although Nile Red accumulates at the same spots, no co-localization with Cy5 is found at the microscopic level, presumably due to the drug release in tumor tissue.

Therefore, Fe3O4-Au Janus NPs represent a unique platform for modern theranostics, comprising the optical visualization capabilities together with studying the cargo and vehicle functions separately and in conjugation, both in vitro and in vivo, for targeted drug delivery.

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P 36

CONTROLLED AGGREGATION OF MAGNETIC NANOPARTICLES FOR NANO-MAGNETOMECHANICAL ACTUATION

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To date, it is clear from numerous researches that mechanotransduction pathways activated by forces from a few to hundreds of piconewtons can be used to control functions of important macromolecules regulating cell metabolism, life and death, i.e. increase proliferation rate, trigger cell apoptosis etc. Nano-magnetomechanical actuation is advantageous strategy of living cells and macromolecules properties manipulation by means of mechanical deformations that imparted by magnetic nanoparticles (MNP) controlled by extremely low frequency non-heating magnetic field. Superparamagnetic nanoparticles are capable of safe circulation and penetration into target tissues and even internalization into cells after intravenous administration, however due to small size ~10-20 nm for magnetite they can generate only moderate forces of tens of piconewtons applied to associated macromolecules in relatively strong alternating magnetic field of about 1 T. Generated forces are proportional to MNP core magnetization, size and magnetic field. But high remanent magnetization materials, as a rule, are much more toxic, particle size is limited by superparamagnetic limit and stronger fields production involves technical complexity. Another possibility to increase mechanical impact is application of ensembles consisting of single superparamagnetic nanoparticles assembled together, such construction has significantly higher magnetic moment. Several papers demonstrate potential of magnetic nanoparticles aggregation for nano-magnetomechanical actuation of biological objects, but for now there is no theoretical basis describing aggregation conditions

The main aim of the current research is development of theoretical models of MNPs aggregation and practical instructions for MNPs design and experimental protocols for both ***in vitro*** and ***in vivo*** application of controlled nanoparticles aggregation and possibly disaggregation.

Main particle-particle interactions and pair potentials governing aggregation processes such as electrostatic repulsion due to the presence of electrical double layer, Van der Waals attraction and magnetic dipole-dipole interaction are estimated. Parameters ranges allowing controlled MNPs aggregation in certain fields and medias are evaluated. Regimes of aggregation kinetics in the absence of field, in static field and in alternating magnetic field are assayed theoretically. Typical magnetic structures of constructed ensembles are assayed by means of computer simulations. Aggregation dynamics depending on magnetic field frequency and amplitude are studied.

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P 37

FTIR-SPECTROSCOPY AS AN EFFECTIVE METHOD FOR EXOSOMAL CONTENT STUDIES

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Today, exosomes are of big interest for scientists. In organism, these vesicles are utilized for cellular communication, genetic information transfer, immune response. Due to the double invagination genesis process, exosomes might be considered as a copy of the cell-producer. This advantage seems to be very perspective in order to provide non-invasive disease diagnostics. Usually, analysis of exosomal type or producer is based on determination of vesicles content, especially proteins and lipids amount. However, for now there is a lack of convenient and express methods for such studies.

In this work, we propose to use FTIR-spectroscopy as an informative and simple method for exosomal content study. Due to complexity of exosomes content, IR-spectra of natural exosomes are rich with signals. We decided that it is reasonable to start our studies with model structures – synthetic exosomes. These are liposomes which lipid content matches exosomal one. Additionally, samples has different amount of bovine serum albumin (BSA) as a model protein, therefore different protein-to-lipid ratio (PtL). In IR-spectra of synthetic exosomes the most intensive absorbance bands refer to CH2-groups of lipids (2853±5 Cm-1 and 2926±5 Cm-1) and amide I of proteins (1660-1610 cm-1). Individual integral intensities of these peaks have difficult dependency from PtL, while intensities ratio (Q) is analytically valuable. The dependence between Q and PtL appeared to be linear. Obtained calibration allowed determining protein-to-lipid content of natural exosomes (0.23 mg proteins / 1 mg lipids).

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SICM-BASED CELL STIFFNESS ANALYSIS OF DRUG-INDUCED ALTERATION IN CELL COMPARTMENTS

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Scanning Ion-conductance Microscopy (SICM) is a novel method of scanning probe microscopy with nanoscale lateral and vertical resolution which allows providing non-invasive in vitro study of single cell in physiologically closed conditions. Through applying intrinsic colloidal pressure between cell membrane and nanopipette tip, non-contact measurement of stiffness is SICM-application can be provided. Stiffness can be measured locally in different parts of cell, caused by small size nanopipette tip, unlike AFM, where large spherical probes are used. Mapping topography and stiffness of non-fixed cells at nanoscale resolution are simultaneous.

Thus, we report cell stiffness analysis of drug-induced alterations in cancer cell compartments studied by SICM. Specifically, we measured human prostate cancer cell line PC3 subjected with paclitaxel for microtubulin stabilization and cytochalasin-D for actin depolymerization. Also, we measured fibrosarcoma cells (HT1080) transfected with Progerin integrated in protein structure of nucleus membrane. Progerin was modified with GFP fluorescent protein (GFP-Progerin). In control and treated PC3 cells, we measured stiffness above the nucleus area and cytoplasm area, which show two different values in control cells (~1.3kPa and ~0.8kPa, respectively). Measured stiffness after paclitaxel treatment shows significantly increased stiffness value on nucleus area and cytoplasm area (~4kPa and ~1.8kPa), whereas cytochalasin-D treatment reduced cell stiffness only on cytoplasm area (~0.5kPa). Experiments with GFP-Progerin carried out in heterogeneous population of HT1080 with control and GFP-Progerin transfected cells. Control stiffness measurement shows ~1.7kPa and ~0.7kPa, while GFP-Progerin treated cells increased value only on nucleus area (~2kPa). All measurements were done in physiological buffer solution (HBSS) at room temperature.

Our results show that stiffness value is different above the nuclei area and cytoplasm area in control cells. Also, microtubulin stabilization and actin depolymerization affect in different way of cell stiffness distribution, Cytochalasin-D treatment decreased stiffness value only on cytoplasm area, but Paclitaxel increased both.

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NEW APPROACH FOR TESTING EFFICIENCY OF NOVEL ANTICANCER DRUGS

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Reactive oxygen species (ROS) is associated with induction of apoptosis. The study of intracellular ROS levels may represent one possibility to research the effects of drugs in inflammatory cells. ROS are released from cells during apoptosis, play a crucial role in the development of cancer and neurodegenerative diseases. Nowadays, there is the problem of developing methods for treating cancer tumors, and quickly evaluation of the anticancer drugs efficiency is the priority. The ROS determination using nanosensors in single cells has gained increasing attention. However, traditional fluorescent dyes have a number of disadvantages. These dyes are known to be intrinsically cytotoxic and thus can significantly alter cellular metabolism.

Here, we have developed an electrochemical method for determining the ROS inside the cells. Using this method, it is possible to evaluate the effect of the developed drugs on the cells. We evaluated the effect of PSMA (Prostate-Specific Membrane Antigen) - specific carrier equipped by Doxorubicin, monomethyl auristatin E or Abiraterone on cell lines with (22RV1) and without (PC-3) PSMA receptors. Our data obtained by using carbon-filled quartz nanopipettes with platinum tips showed a ROS increase using conjugates compared with native drugs. We also studied the effect of drugs based on copper complexes on the cell line MCF-7 and demonstrated that complexes with copper in various degrees of oxidation, depending on the ligands, can have different effects on tumor cells. Complexes with copper in various degrees of oxidation, depending on the ligands, can have different effects on tumor cells. In the future, this method may allow evaluating the effect of drugs in vitro and to help validate drug candidates for preclinical evaluation.

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MANAGEMENT OF ENZYMATIC ACTIVITY OF PAMO IMMOBILIZED ONTO HYBRID MAGNETITE-GOLD NANOPARTICLES UNDER LOW-FREQUENCY MAGNETIC FIELD

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Phenylacetonemonooxygenese (PAMO) is an enzyme of Baeyer-Villiger family that catalyzes the conversion of phenylacetone to phenylacetate using molecular oxygen and NADPH. It contains FAD-binding and NADP-binding domains divided by a very conservative motif consisting of 11 amino acids called fingerprints (residues 167-177). Malito et. al [1] showed that His-173 is very crucial for catalysis and FAD binding. This residue is fully solvent exposed and together with fingerprint motif residues are likely to have a critical role by taking part in the domain rotations and conformational changes that occur during the catalytic cycle.

Magneto-nanomechenical approach involves macromolecule structure local deformation via mechanical actuation of functionalized magnetic nanoparticles by non-heating low frequency magnetic field (LF MF) [2]. For experiment, hybrid magnetite-gold nanoparticles (M-GNP) were synthesized according to [3]. Gold surface of M-GNP was then modified with nitrilotriacetic acid (NiTriA) which can form complex with Ni2+, after that PAMO was immobilized through poly-histidine (6xHis) sequence binding onto Ni-NiTriA surface G-MNP. All steps of M-GNP synthesis, surface modification and enzyme immobilization were monitored by NTA (nanoparticle tracking analysis) method and TEM photos.

On the last step of our work, we studied impact of LF MF (50 Hz 100 mT) on the catalytic activity of immobilized PAMO. Before being exposed onto LF MF, PAMO activity was extremely low. Turning on the LF MF lead to 2-2,5 times increase of PAMO activity. We think that, as a result of PAMO immobilization onto G-MNP, His-173 could be bound to nanoparticles surface via Ni-NiTriA too leading to the loss of the enzyme activity. Forces, resulting from rotation of G-MNP under LF MF, could help desorption of His-173 from nanoparticles surface permitting the restoration of PAMO catalysis.

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FTIR-SPECTROSCOPY AS AN EFFECTIVE METHOD FOR EXOSOMAL CONTENT STUDIES

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Today, exosomes are of big interest for scientists. In organism, these vesicles are utilized for cellular communication, genetic information transfer, immune response. Due to the double invagination genesis process, exosomes might be considered as a copy of the cell-producer. This advantage seems to be very perspective in order to provide non-invasive disease diagnostics. Usually, analysis of exosomal type or producer is based on determination of vesicles content, especially proteins and lipids amount. However, for now there is a lack of convenient and express methods for such studies.

In this work, we propose to use FTIR-spectroscopy as an informative and simple method for exosomal content study. Due to complexity of exosomes content, IR-spectra of natural exosomes are rich with signals. We decided that it is reasonable to start our studies with model structures – synthetic exosomes. These are liposomes which lipid content matches exosomal one. Additionally, samples has different amount of bovine serum albumin (BSA) as a model protein, therefore different protein-to-lipid ratio (PtL). In IR-spectra of synthetic exosomes the most intensive absorbance bands refer to CH2-groups of lipids (2853±5 Cm-1 and 2926±5 Cm-1) and amide I of proteins (1660-1610 cm-1). Individual integral intensities of these peaks have difficult dependency from PtL, while intensities ratio (Q) is analytically valuable. The dependence between Q and PtL appeared to be linear. Obtained calibration allowed determining protein-to-lipid content of natural exosomes (0.23 mg proteins / 1 mg lipids).

This work was supported by Russian Foundation for Basic Research grants: 17-54-33027 and 18-29-09154. The samples of natural exosomes were kindly provided by Dr. E.V.

P 42

NEW ECOLOGICAL PURE FERTILIZER IN AGRICULTURE

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The chemical fertilizers and pesticides used in agriculture around the world harm both the environment and the health of living things to a great extent. Accordingly, ecological pure fertilizers are needed organic-mineral fertilizer «Georost» has these properties. «Georost» was taken from decayed deciduous wood and ultrasonic crushing (fracture) process was performed in water environment. The active substance of manure is humic acids. It activates all life processes of the plant as biostimulants, improves the quality of the soil and makes it a healthy state. This preparation is applied to the soil in spring and spring and applied to plants (leaves and plantings) as liquid additional fertilizers during the vegetation period. «Georost» is used industrially in agriculture and farms in agriculture and farms in the republics of Russia and Belarus.

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TESTING THE EFFECTS OF SILVER NANOPARTICLES IN IN VITRO MODELS OF INTESTINAL TOXICITY AND INFLAMMATION

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Silver nanoparticles (AgNPs) are among the most widely used nanomaterials, resulting in high human exposure, especially through the oral route. This may happen via incorporation of AgNPs in all phases of food production (processing, packaging and storage) to prevent bacterial proliferation, or/and via food supplements, marketed as health supplements, available in grocery and online stores. Therefore, it is of outmost importance to extensively evaluate the potential health impact of AgNPs, namely in the gastrointestinal system. In that sense, it was our aim to test the potential toxic effects of AgNPs [two different sizes (4 and 19 nm), coated with one of the most traditional polycationic polymers, polyethylenimine (PEI)], in an in vitro model of intestinal cells (Caco-2 cells), and in an in vitro model of cells intrinsically involved in intestine inflammatory process (human neutrophils). Our results showed that AgNPs significantly affect cell viability and the integrity of Caco-2 cell monolayers. The production of reactive species was measured by two fluorescent probes, dihydrorhodamine 123 (DHR) and dichlorodihydrofluorescein diacetate. The lack of response of intestinal epithelial cells treated with AgNPs suggested that the production of reactive species did not constitute a cell death mechanism. On the other hand, we observed that AgNPs induced the production of reactive species by human neutrophils via NADPH oxidase, through the activation of PKC. This work prompts us to further explore the molecular mechanisms underlying AgNPs toxicity and inflammation at the intestinal level.

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ACUTE TOXICITY OF THE NOVEL RECOMBINANT GROWTH FACTORS S-TAG-BMP-2 AND EPO-HBD IMMOBILIZED ON THE DEMINERALIZED BONE MATRIX IN MICE

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The objective of this study is to evaluate acute toxicity of the novel recombinant Bone Morphogenetic Protein 2 with an additional s-tag domain (s-tag-BMP-2) and EPO-HBD fusion protein consisting of sequences of human erythropoietin (EPO) and the heparin-binding protein domain (HBD) from Bone Morphogenetic Protein 2 that were immobilized on the demineralized bone matrix (DBM).

Both EPO-HBD and s-tag-BMP-2 were expressed in Escherichia coli and extracted from the inclusion bodies. Following purification and refolding proteins were bound to DBM disks of 1.5 (thickness) x 4 (diameter) mm and sterilized. Study of toxic effects was carried out in inbred CBA mice line (4-6 weeks old, average weight18.7±1.3 g, n=40). For this study, there were four experimental groups each consisting of five male and five female mice. The first group of 10 intact animals served as the control. The second and third groups received DBM with s-tag-BMP-2 (10 mkg) and with EPO-HBD (10 mkg) respectively. The fourth group was administered by DBM with both recombinant proteins with the same dosages.

Composite materials were administered by single subcutaneous implantation.Following the two-weeks healing interval, toxic effects were assessed using clinical and laboratory diagnostic methods: clinical examination and observation, assessment of body weight dynamics, hematological and biochemical blood analysis, and pathologic anatomical research with the determination of mass coefficients of internal organs.

Compared to the control group none of the experimental groups registered induced changes in body weight, food intake, clinical signs, and zoosocial behavior. None of the composite materials caused any death. There were no changes in the level of enzymes, bilirubin, and the protein and carbohydrate metabolism in the body. There were single statistically significant changes in the clinical blood parameters of the third and fourth experimental groups which are specific to the activity of erythropoietin. The pathoanatomical analysis showed no abnormalities in the anatomical structure of organs, and there were no differences in mass coefficients.

The results of this study show that s-tag-BMP-2 and EPO-HBD immobilized on the demineralized bone matrix did not induce any remarkable toxic response in mice and are biologically safe.

This work was supported by the Russian Science Foundation (Grant No. 16-15-00133).

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A SANDWICH-TYPE IMMUNOCOMPLEX BASED ON CORE-SHELL MICROBEADS AND SERS NANOTAGS ENABLES CANCER-DERIVED EXOSOME DETECTION

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Exosomes have emerged as a new class of cancer biomarkers with great potential to diagnose cancer in its early stages with high efficiency [1]. A sandwich-type immunocomplex based on antibody functionalized microbeads and plasmonic nanoparticles has been shown to be an effective approach for the detection of various types of cancer markers [2]. In this work we developed a new platform to capture exosomes derived from Skov3 cell lines using core-shell microbeads and SERS nanotags. The core-shell microbeads represent silica microparticles with gold nanostars grown on the bead surface (Fig. 1a). SERS nanotags are gold nanorods (AuNR) with the cresyl violet Raman reporter incorporated into the cetyltrimethylammonium bromide (CTAB) bilayer. To specifically capture exosomes, EpCAM primary antibody was introduced on the surface of both core-shell microbeads and SERS nanotags containing mercaptobenzoic acid using carbodiimied-mediated synthesis. The sandwish-type immunocomplex was formed by mixing core-shell microbeads and Skov3 exosomes, and then SERS nanotags were added to the mixture. The complex formation was monitored by acquiring SERS spectra in a solution using a portable Raman spectrometer MiniRam (B&WTek, USA) (Fig. 1b). We anticipate that the results from this work can be useful to probe exosomes in complex media or in a sample with different populations of exosomes.

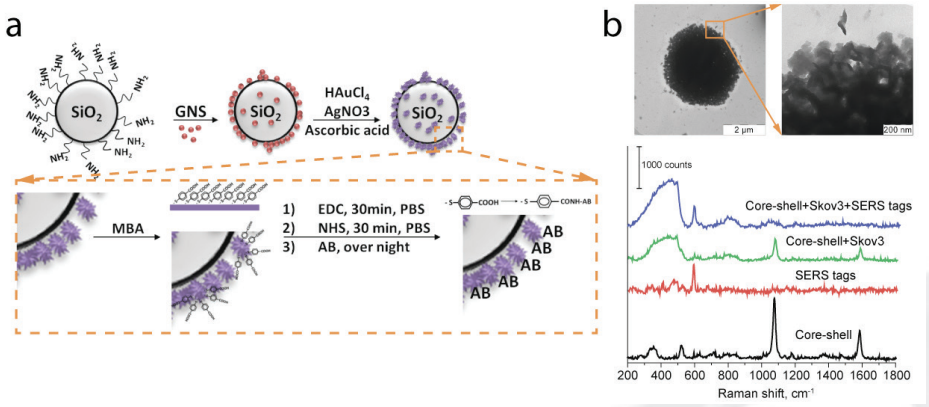

Fig.1 (a) Schematics depicting fabrication of gold nanostars on the surface of amino-silica microbeads and their subsequent fictionalization with EpCam antibody. (b) TEM images of the immunocomplex between core-shell microbeads, Skov3 exosomes, and SERS nanotags (top row) and SERS spectra of the immunocomplex and control samples (bottom row).

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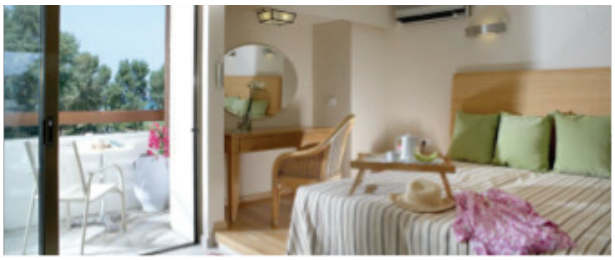

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