BIONANOTOX 2012

"BIOMATERIALS AND BIONANOMATERIALS: RECENT PROBLEMS AND SAFETY ISSUES"

3rd Russian - Hellenic Symposium with International Participation and Young Scientists School

Included

Advanced Research Workshop on Nanotechnologies & Bioanalytical Advances for improved Public Security and Enviromental Safety and Health

6-13 MAY, 2012

Heraklion, Crete, Greece

UNIVERSITY OF CRETE

D. MENDELEYEV UNIVERSITY OF CHEMICAL TECHNOLOGY OF RUSSIA

M. LOMONOSOV MOSCOW STATE UNIVERSITY

M.SHEMYAKIN AND YU.OVCHINNIKOV INSTITUTE OF BIOORGANIC CHEMISTRY

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HELLENIC SOCIETY OF TOXICOLOGY

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E U R O T O X

Final Program/Abstract Book

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UNIVERSITY OF CRETE

D. MENDELEYEV UNIVERSITY OF CHEMICAL TECHNOLOGY OF RUSSIA

HELLENIC SOCIETY OF TOXICOLOGY

Welcome Letter

On behalf of the organizing committee of the 3rd Russian-Hellenic Symposium with International Participation and Young Scientists School " Biomaterials and Bionanomaterials:Recent Problems and Safety Issues" included Advanced Research Workshop on Nanotechnologies & Bioanalytical Advances for Improved Public Security and Enviromental Safety and Health, we are privileged to invite you to grace with your presence and participation the works of the Symposium, which is to be held in Heraklion, in the beautiful island of Crete, in May 2012.

Crete is an island with numerous coves, bays, peninsulas, and sandy beaches along the beautifully blue Mediterranean Sea. After all, it's among the finest in the world and has established Crete as one of Europe's most popular holiday destinations. And, of course, the island's historic importance in today's world as Knossos, Phaistos and Gortys, is evidenced by the tens of thousands of visitors to these sites each year. Located almost in the centre of Crete, Heraklion has since the early years played a significant part in the history of the island. The theme of the Symposium concerns one of the most progressing directions of science and technology. BioNanoToxicology Issues lie at the interface of many disciplines, ranging from biology to chemistry, toxicology, computational science chemistry, nanotechnology and biotechnology

The Symposium is a continuation of a long term co-operation between Russian and Hellenic scientists in this field that has been ongoing for the last 20 years, in the frame of the bilateral scientific state programs.
The International Advisory Board of the Symposium is chaired by E.P.Giannelis, Department Chair, Department of Materials Science and Engineering, Cornell University, S.P.Anastasiadis, Professor, Foundation for Research and Technology -Hellas (FO.R.T.H.), Institute of Electronic Structure and Laser (I.E.S.L.), V.Torchilin Professor, Director of Center of Pharm. Biotech & Nanomedicine, Northeastern University, Boston, USA, D.A.Spandidos Professor of Virology, Medical School, University of Crete, Heraklion, Greece, P. Sarkisov Academician of RAS, President of D. Mendeleyev University of Russia, Moscow, Russia and A. Khokhlov Academician of RAS, Vice-Rector of M. Lomonosov Moscow State University, Moscow, Russia.

It is anticipated that scientists from the Russian Academy of Science, the most prominent Universities as well as Technological Institutes and Companies and distinguished field specialists coming form many countries will attend the symposium. Reduced registration rates will be provided, in order to enable more young scientists to attend the Symposium.
At this symposium the attendee will have the chance to meet important representatives of research in the field, discuss with them and exchange ideas. This will accomplish the aim of the symposium, which is the generation of new and vigorous interactions between the different aforementioned disciplines, which will have enormous positive effects in our societies.

We invite you all to participate to our Symposium. Crete will welcome you with its smiling Cretan sun, the sounds of the Cretan lyre, the scents of orange blossom and jasmine, a slice of cool red watermelon and a glass of iced raki.

Co-Chairmen of the Organizing Committee

Aristidis Tsatsakis, PhD, DSc, ERT

Mikhail Shtilman, PhD, DSc

Committees

Co-President

Emmanuel P. Giannelis	**Spiros H. Anastasiadis**	**Torchilin Vladimir**
Demetrios A. Spandidos	**Sarkisov Pavel**	**Khokhlov Alexey**

International Advisory Board

Co-President	Giannelis Emmanuel P.	Department Chair, Department of Materials Science and Engineering, Cornell University
Co-President	Anastasiadis Spiros H.	Professor, Foundation for Research and Technology - Hellas (FO.R.T.H.), Hellas Department of chemistry University of Crete, Institute of Electronic Structure and Laser (I.E.S.L.)
Co-President	Torchilin Vladimir	Professor, Director of Center of Pharm. Biotech & Nanomedicine, Northeastern University, Boston, USA
Co-President	Spandidos Demetrios A.	Professor of Virology, Medical School, University of Crete, Heraklion, Greece
Co-President	Sarkisov Pavel	Academician of RAS, President of D. Mendeleyev University of Russia, Moscow, Russia
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	Lappas Alexander	Principal Researcher, Foundation for Research and Technology, Crete
	Neufeld Ron	Professor, Queen's University, Kingston, Ontario, Canada
	Ozerin Alexander	Corresponding member of RAS, Director of N. Enikolopov Institute of Synthetic Polymeric Materials of RAS, Moscow, Russia
	Panarin Eugenie	Corresponding member of RAS, Director of Institute of Macromolecular Compounds of RAS, St. Petersburg, Russia
	Poncelet Denis	Professor, ONIRIS, UMR CNRS GEPEA 6144, Nantes, France
	Rizos Apostolos	Professor, Department of Chemistry, University of Crete, Iraklion, Greece
	Tkachuk Vsevolod	Academician of RAS and RAMS, Dean of Faculty of Fundamental Medicine, M. Lomonosov Moscow State University, Moscow, Russia
	Tsakalof Andreas	Professor, Medical Chem. Dep., University of Thessaly, Larissa, Greece
	Varfolomeev Sergey	Corresponding member of RAS, Director of N. Emanuel Institute of Biochemical Physics of RAS, Moscow, Russia
	Ulbrich Karel	Professor, Head of Dept. of Biomedicinal Polymers, Institute of Macromolecular Chemistry, Prague, Czech Republic
	Zezin Alexander	Corresponding member of RAS, Head of Chair, M. Lomonosov Moscow State University, Moscow, Russia

Organizing Committee

Co-chairman of Symposium Tsatsakis Aristidis	Professor, Director of Forensic Sciences & Toxicology Dep., University of Crete, Iraklion, Greece
Co-chairman of Symposium Shtilman Mikhail	Professor, Head of Center "Biomaterials", D.Mendeleyev University of Chemical Technology of Russia, Moscow, Russia
Eremin Sergey	Professor, M.Lomonosov Moscow State University, Moscow, Russia
Klyachko Natalia	Professor, M.Lomonosov Moscow State University, Moscow, Russia
Markvicheva Elena	Professor, M.Shemyakin-Yu.Ovchinikov Institute of Bioorganic Chemistry, Moscow, Russia
Shashkova Irina	PhD, Senior scientific worker, D.Mendeleyev University of Chemical Technology of Russia, Moscow, Russia
Shishatskaya Ekaterina	Professor, Head of Chair Medical Biology, Siberian Federal University, Krasnoyarsk, Russia
Stivaktakis Polychronis	PhD, Research Scientist, University of Crete, Iraklion, Greece
Tzatzarakis Manolis	PhD, Senior scientific worker, University of Crete, Iraklion, Greece
Vamvakaki Maria	Ascociate Professor, Department of Materials Science and Technology, University of Crete
Vynias Dionysios	PhD, Research Scientist, University of Crete, Iraklion, Greece

Scientific program

Sunday, May 6, 2012

Arrival – Registration

20.00	Welcome Cocktail

Monday, May 7, 2012

08.00-09.30	Breakfast
10.00	OPENING CEREMONY
10.00	**OPENING CEREMONY**
10.00-10.10	**WELCOME ADDRESS** **A. M. Tsatsakis, Co-head of Organizing Committee** University of Crete, Iraklion, Crete, Greece
10.10-10.20	**WELCOME ADDRESS** **S. H. Anastasiadis, Co-President of Symposium** Institute of Electronic Structure and Laser, Iraklion, Crete, Greece
10.20-10.30	**ABOUT SYMPOSIUM PROGRAM** **M. I. Shtilman, Co-head of Organizing Committee** D. Mendeleyev University of Chemical Technology of Russia, Moscow, Russia
10.30-11.10	***OPENING LECTURES*** **NANOPREPARATIONS TO BRING DRUGS INSIDE CELLS AND TO INDIVIDUAL ORGANELLES** **V. Torchilin, Co-President of Symposium** Northeastern University, Boston, USA
11.10-11.30	**Coffee break, Poster session**
11.30-12.30	***MORNING SESSION***
	Chairmen: Prof. V. Torchilin, Prof. S. Varfolomeev
11.30-12.00	**IMMOBILIZED ENZYMES. NEW APPLICATIONS** **S. Varfolomeev** N.Emanuel Institute of biochemical physics, Moscow, Russia

12.00-12.30	**CYTOCHROME C- CARDIOWPIN COMPLEX: A LIPOPROTEIN NANOSTRUCTURE THAT TURNS ON THE CASCADE OF REACTIONS TERMINATED BY SELF-DESTRUCTION OF LIVING CELLS** **Y.A. Vladimirov[1,2], A.V. Alekseev[1], V.V. Volkov[2], B.A. Nabatov[2]** [1]Moscow State University, Russia, [2]Institut of Crystallography of Russian Academy of Science, Moscow, Russia
12.30-13.00	**ANTIVIRAL PEPTIDE NANOCOMPLEXES AS NOVEL THERAPEUTIC MODALITY** **T. Bronich** College of Pharmacy and Center for Drug Delivery and Nanomedicine, University of Nebraska Medical Center, Omaha, NE, USA
13.00-14.00	**Lunch**
14.00-16.30	**Break**
16.30-18.00	***EVENING SESSION - Young Scientists Session***
	Chairmen: Prof. E. Shishatskaya, Prof. E. Markvicheva
16.30-16.50	**RESORBABLE BIOCERAMICS FABRICATED FROM THERMOLYSED OCTACALCIUM PHOSPHATE (OCP)** **E.V. Kukueva, T.V. Safronova, B.R. Tshuragulov, V.I. Putlayev** Lomonosov Moscow State University, Moscow, Russia
16.50-17.10	**CELL-FREE PRODUCTION OF VOLTAGE-SENSING DOMAIN FROM HUMAN NAV1.4 CHANNEL FOR FUNCTIONAL AND STRUCTURAL STUDIES** **E.N. Lyukmanova, M.A. Shulepko, I.O. Butenko, Z.O. Shenkarev, A.S. Paramonov, D.A. Dolgikh, M.P. Kirpichnikov** Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia
17.10-17.30	**EFFECT OF PLASMA H_2O_2 TREATED ON SURFACE PROPERTIES OF POLYHYDROXYALKANOATES** **E.D. Nikolaeva[1], D.B. Goncharov[2]** [1] Laboratory of HAB Institute of Biophysics SB RAS, Krasnoyarsk, Akademgorodok 50/50 [2] Siberian Federal University, Krasnoyarsk, Russia
17. 30-17.50	**FEATURES OF BOTH STRUCTURE AND FUNCTIONING OF THE ENZYME LYSK ANTYSTAPHYKOCOCCAL BACTERIOLYTIC NANOZYMES** **L.Yu. Filatova[1], D.M. Donovan[2], S.C. Becker[2], D.N. Lebedev[1], E.V. Koudriachova[1], A.V. Kabanov[1], N.L. Klyachko[1]** [1]M.V. Lomonosov Moscow State University, Moscow, Russia [2]ARS-USDA Beltsville Agricultural Research Center, USA
18.00-19.00	**Break**
19.00-20.00	**Dinner**

Tuesday, May 8, 2012

08.00-09.30 **Breakfast**

09.30-12.30 ***MORNING SESSION***

Chairmen: Prof. T. Bronich, Prof. Yu. Vladimirov

09.30-10.00 **CHITIN AND CHITOSAN NEW PROSPECTS AND OLD PROBLEMS**
V.P. Varlamov, A.V. Il'ina, S.A. Lopatin, A.N. Levov, D.V. Kurek, A.A. Zubareva
Centre "Bioengineering", Russian Academy of Sciences, Moscow, Russia

10.00-10.30 **SEAWEEDS AND THEIR DERIVATIVES ARE AN INEXHAUSTIBLE SOURCE OF BIOPOLYMERS FOR BIOTECHNOLOGY DRUGS, FOOD SUPLEMENTS AND BIOLOGICALLY ACTIVE ADDITIVES**
AV Podkorytova
Russian Federal Research Institute of Fisheries and Oceanography,
17, V. Krasnoselskaya, 107140, Moscow, Russia, e-mail: podkor@vniro.ru

10.30-11.00 **SYNTHESIZED NANO AND MICROFIBER MATRIX NETWORKS SUPPORT IMMUNOISOLATED PANCREATIC ISLETS FOR IMPLANTATION**
J.A.M. Steele[1], E. Carmona[2], J-P. Halle[2], A.E. Barron[3] and R.J. Neufeld[1]
[1]Queen's University, Kingston, Ontario, Canada (neufeld@queensu.ca)
[2]Université de Montréal, Maisonneuve Rosemont Hospital Research Centre
[3]Stanford University, Palo Alto, CA

11.00-11.30 **IN VITRO HEMOCOMPATIBILITY OF NANOCARRIERS TAILORED FOR BIOPHARMACEUTICAL DRUGS**
Ch. Sevrin, B. Cerda, L. Flebus, F. Lombart and Ch. Grandfils*
Interfacultary Research on Biomaterials (CEIB), University of Liege, Chemistry Institute, B6C, B-4000 Liège (Sart-Tilman), Belgium. C.Grandfils@ulg.ac.be

11.30-12.00 **Coffee break, Poster session**

Chairmen: Prof. V. Varlamov, Prof. A.Podkorytova

12.00-12.30 **THE SYNTHESIS OF METAL NANOPARTICULATE CATALYSTS WITHIN RESPONSIVE MICROGELS**
S. H. Anastasiadis
Institute of Electronic Structure and Laser, Foundation for Research and Technology - Hellas and Department of Chemistry, University of Crete, Greece

12.30-13.00 **"SMART" POLYMERS FOR NUCLEAR MEDICINE**
V.R Duflot, E.A. Dubova, N.M. Bolbit, E.I. Lobanova
Branch of Karpov Institute of Physical Chemistry, Scientific and Production Centre, Obninsk, Russia

13.00-14.00 **Lunch**

14.00-16.30 **Break**

16.30-18.00 ***EVENING SESSION***

Chairmen: Prof. N.Klyachko, Prof. V.Duflot

16.30-17.00 **PHOTO-SENSITIVE POLYMERIC MATERIALS FOR BIOMEDICAL APPLICATION**
M. Vamvakaki
Dept. of Materials Science and Technology, Univ. of Crete, Iraklion, Greece

17.00-17.30 **TUMOUR-TARGETED POLYMER CARRIERS BASED ON STAR HPMA COPOLYMERS PREPARED BY RAFT POLYMERISATION**
P. Chytil, M. Bittner, T. Etrych, K. Ulbrich
Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, v.v.i., Heyrovský Sq. 2, 162 06, Prague 6, Czech Republic

17.30-18.00 **SYNTHESIS OF WELL-DEFINED SEMITELECHELIC *N*-(2-HYDROXYPROPYL)-METHACRYLAMIDE POLYMERS BY RAFT POLYMERIZATION**
V.Šubr, L.Kostka, J.Strohalm, K.Ulbrich
Institute of Macromolecular Chemistry Academy of Sciences of the Czech Republic, v.v.i., Prague, Czech Republic

18.00-19-00 **Break**

19.00-20.00 **Dinner**

Wednesday, May 9, 2012

08.00-09.30 **Breakfast**

10.00-13.00 ***MORNING SESSION***

Chairmen: Prof. B.B.Dzantiev, Prof. R.Neufeld

09.30-10.00 **COMPARATIVE STUDY OF WIDE TAXONOMIC NATURAL CORALS FOR BONE TISSUE RECONSTRUCTION AND ENGINEERING**
I.K. Sviridova[1], N.S. Sergeeva[1], S.M. Barinov[2], V.S. Komlev[2], V.A. Kirsanova[1], S.A. Akhmedova[1], I.V. Fadeeva[2], Ja. D. Shansky[1]
[1] Moscow P.A. Herzen Research Oncological Institute, Moscow, Russia
[2] A.A. Bajkov Institute of Metallurgy an Material Science of Russian Academy of Sciences, Moscow, Russia

10.00-10.30 **TARGETED POLYMER THERAPEUTICS WITH A COILED COIL MOTIF**
M.Pechar[1], R.Pola[1], K.Ulbrich[1], L.Bednárová[2], P.Maloň[2], I.Sieglová[3], V.Král[3], M.Fábry[3], M.Kabešová[4], M.Kovář[4]
[1]Institute of Macromolecular Chemistry, AS CR, Prague, Czech Republic
[2]Institute of Organic Chemistry and Biochemistry, AS CR, Prague, Czech Republic
[3]Institute of Molecular Genetics, AS CR, Prague, Czech Republic
[4]Institute of Microbiology, AS CR, Prague, Czech Republic

10.30-11.00 **BIODEGRADABLE PHAS: PRODUCTION, BIOMEDICAL INVESTIGATIONS, APPLICATIONS**
E.I. Shishatskaya[1,2]
[1] Siberian federal University, Krasnoyarsk, Russia
[2] Institute of Biophysics SB RAS, Krasnoyarsk, Russia

11.00-11.30 **LABELING OF BIOLOGICALLY ACTIVE POLYMER (POLY-N-VINYLPYRROLYDONE) DERIVATIVES WITH "COLD" Re AND "HOT" ^{99m}Tc AND ^{161}Tb.**

N.I. Gorshkov[1], A.Yu. Murko[1], Yu.I. Zolotova[1], O.V. Nazarova[1], I.I. Malakhova[1], V.D. Krasikov [1], P.S. Chelushkin[1], Yu.E. Moskalenko[1] , S.V. Burov [1], M. Behe[2], R. Schibli[2] B.G. Kabulov[3] and E.F. Panarin[1]

[1]Institute of Macromolecular Compounds RAS, St.-Petersburg, 199004, Bolshoi pr. V.O., 31, Russia

[2] Institute for Pharmaceutical Sciences ETH Hönggerberg, HCI H425 Wolfgang-Pauli-Strasse 10 CH.8093 Zurich, Switzerland

[3] Tashkent State Technical University, Tashkent, Uzbekistan

11.30-12.00 **Coffee break, Poster session**

Chairmen: Prof. M.Pechar, Prof. A.K. Tsakalof

12.00-12.30 **STRUCTURE AND MECHANICAL PROPERTIES OF ULTRAFINE GRAINED TITANUM PRODUCED BY THE SEVERE PLASTIC DEFORMATION AND ITS MEDICAL APPLICATION**

Yu. P. Sharkeev, A. Yu. Eroshenko

Institute of Strength Physics and Materials Science, SB RAS, Tomsk, Russia

12.30-13.00 **POROUS BIORESORBABLE CERAMICS BASED ON CALCIUM PYROPHOSHATE AND POLYPHOSPHATES**

S.A. Korneychuk[1], T.V. Safronova[2], V.I. Putlyaev[1]

[1]Lomonosov Moscow State University, Department of Materials Science, Moscow, Russia

[2]Lomonosov Moscow State University, Department of Chemistry, Moscow, Russia

13.00-14.00 **Lunch**

14.00-16.30 **Break**

16.30-18.00 ***EVENING SESSION- Young Scientists Session***

Chairmen: Prof. M.A. Myagkova, Prof. E.Markvicheva

16.30-17.00 **T1-CONTRAST AGENT BASED ON MONOCLONAL ANTIBODY FOR MRI VISUALIZATION OF TUMOR CELLS OF GLIOMA**

T.O. Sandalova[1,2], N.V. Nukolova[2,3], M.A. Abakumov[1], N.F. Grinenko[3], D.A. Bychkov[4], S.A. Shein[1], A.Y. Morozova[3], A.V. Kabanov[2,5], V.P. Chekhonin[1,3]

[1] Russian State Medical University, Moscow, Russia

[2] Lomonosov Moscow State University, Department of Chemistry, Moscow, Russia

[3] Serbsky State Scientific Center for Social and Forensic Psychiatry, Moscow, Russia

[4] Lomonosov Moscow State University, Department of Geology, Moscow, Russia

[5] University of Nebraska Medical Center, Omaha, USA

17.00-17.30 **SURFACE MODIFICATION OF POLYMERIC BIOMATERIALS BY LOW-TEMPERATURE PLASMA TO CONTROL CELL AFFINITY**

T. Demina[1], D. Zaytseva-Zotova[2], M. Yablokov[1], A. Gilman[1], T. Akopova[1], E. Markvicheva[2], A. Zelenetskii[1]

[1] Enikolopov Institute of Synthetic Polymer Materials, Russian Academy of Sciences, Profsoyuznaya Str., 70, 117393 Moscow, Russia

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

17.30-18.00 **GLIOMA C6 VISUALIZATION BY MRI WITH CONJUGATE OF MAGNETIC IRON OXIDE NANOPARTICLES AND MONOCLONAL ANTIBODIES TO VEGF**

M.A. Abakumov[1], H. Vishwasrao[3], T.O. Sandalova[1], N.V. Nukolova[2], N.F. Grinenko[2], M. Sokolsky-Papkov[3], A.V. Kabanov[3,4], V.P. Chekhonin[1,2]
[1]RSMU, Chair of medical nanobiotechnology, Moscow, Russia.
[2]Center for Social and Forensic Psichiatry, Department of fundamential and applied neirobiology, Moscow, Russia
[3]Center for Drug Delivery and Nanomedicine, Medical Center of University of Nebraska, Nebraska, Omaha
[4]Moscow State University, Department of Chemistry, Chair of Chemical enzimology, Moscow, Russia.

18.00-19.00 **Break**

19.00-20.00 **Dinner**

Thursday, May 10, 2012

08.00-09.00 **Breakfast**

Workshop: "Nanotechnologies and Bioanalytical Advances for improved Public Security and Environmental Safety and Health"
***Moderator*: Prof. A. Tsatsakis, Co-head of Organizing Committee, Vice-President of European Toxicology Society**

10.00-13.00 ***MORNING SESSION***

Chairmen: Prof. S.Eremin, Prof. B.B.Dzantiev

10.00-10.30 **METHODS OF STUDY OF TOXICOLOGY OF NANOBIOMATERIALS**

A.A.Tsatsakis
University of Crete, Iraklion, Greece

10.30-11.00 **APPLICATION OF MANUFACTURING NANOPARTICLES FOR THE DETECTION OF BIOLOGICALLY ACTIVE COMPOUNDS**

B.B. Dzantiev
Institute of Biochemistry Russian Acad. Sci., Moscow, Russia

11.00-11.30 **NEW POSSIBLE IMMUNOLOGICAL MARKERS IN DIAGNOSTICS OF ADDICTIVE STATES: DRUG ADDICTION, ALCOHOLISM, PATHOLOGIC GAMBLING**

M.A. Myagkova, V.S. Morozova, V.V. Shipitsyn, S.N. Petrochenko, E.A. Bryun
Moscow Research and Practical Center for Narcology of Moscow Health Department, Moscow, Russia

11.30-12.00 **Coffee break, Poster session**

Chairmen: Prof. A.A.Tsatsakis, Prof. I.Kurochkin

12.00-12.30 **ANTIBODIES TO OPIATES IN SERUM AS MARKERS OF CHRONIC DRUG USE**

M. Tzatzarakis[1], V. Morozova[2], E. Vakonaki[1], S. Petrochenko[2], M. Myagkova[2], E. Barbounis[1], A. Kanaki[1], S. Belivanis[1], A. Tsatsakis[1]
[1]Laboratory of Toxicology, University of Crete, Iraklion, Greece
[2]Russian Academy of Science Institute for Physiologically Active Compounds, Moscow, Russia.

Thursday, May 10, 2012

12.30-13.00 **MODERN IMMUNOCHEMICAL METHODS OF DETECTION OF POISONS AND TOXICANTS**
S.A. Eremin
M. Lomonosov Moscow State University, Moscow, Russia

13.00-13.30 **APPLICATION METHODS OF ANALYTICAL TOXICOLOGY AND CLINICAL DIAGNOSTICS AT THE EXOGENOUS POISONING**
L.U.Kislun[1], G.N.Ilchenko[1], U.V. Kislun[2], S.A.Savchuk[2]
[1]Clinical hospital No 123 FMBA, Odintsovo, Russia
[2]National Science Center of Narcology, laboratory of toxicology, Moscow, RussiaM. Lomonosov Moscow State University, Moscow, Russia

13.30-14.00 **Lunch**

14.00-17.00 **Break**

17.00-18.00 ***EVENING SESSION***

Chairmen: Prof. M.Tzatzarakis, Prof.S.Eremin

17.00-17.30 **ORGANIZED FILMS BASED ON PHOTOSENSITIVE MEMBRANE PROTEINS AS THE KEY ELEMENTS OF NANO–BIO HYBRID STRUCTURES**
S. Yu. Zaitsev[1], D. O. Solovyeva[1], I. Nabiev[1,2]
[1]Laboratory of Nano-Bioengineering, Moscow Engineering Physics Institute, Moscow, Russian Federation
[2]European Technological Platform "Semiconductor Nanocrystals", Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland

17.30-18.00 **LIPID-PROTEIN NANODISCS: ALTERNATIVE TOOL FOR PRODUCTION, STABILIZATION, STRUCTURE-FUNCTIONAL STUDIES AND DELIVERY OF MEMBRANE BIOMOLECULES**
Z.O. Shenkarev, E.N. Lyukmanova, A.S. Paramonov, A.S. Arseniev
Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russia

18.00-19.00 **Break**

19.00-20.00 **Dinner**

Friday, May 11, 2012

Friday, May 11, 2012

08.00-09.00 **Breakfast**

09.30 ***MORNING SESSION***

Chairmen: Prof. E.Markvicheva, Yu. Sharkeev

09.30-10.00 **DEVELOPMENT OF IMPLANTABLE BIOMATERIALS FOR BONE TISSUE ENGINEERING**
M. Chatzinikolaidou
Dept. of Materials Science and Technology, Univ. of Crete, Iraklion, Greece

10.00-10.30 **COMPUTER ASSISTED SELECTION OF OPTIMAL MONOMER FOR IMPRINTING OF TRI-O-ACETYLADENOSINE IN POLYMER MATRIX**
Y. Douhaya[1], V.Barkaline[1], A.Tsakalof[2]
[1] - Belarusian National Technical University, Minsk, Belarus
[2] - University of Thessaly, Larisa, Greece

10.00-10.30 **MICROBIAL SYNTHESIS AND PROPERTIES OF 3-HYDROXYBUTYRATE AND 4-HYDROXYBUTYRATE COPOLYMERS**
N. O. Zhila
[1]Siberian Federal University, Krasnoyarsk, Russia
[2]Institute of Biophysics SB RAS, Krasnoyarsk, Russia

10.30-11.00 **MULTICELLULAR TUMOR SPHEROIDS FORMATION IN POLYELECTROLYTE MICROCAPSULES USING RGD-PEPTIDES**
D. Zaytseva-Zotova[1], R. Akasov[1], I. Chevalot[2], A. Marc[2], S. Burov[3], E. Markvicheva[1]
[1]Shemyakin-Ovchinnikov institute of bioorganic chemistry RAS, Moscow, Russia
[2]Laboratoire des Sciences du Génie Chimique, UPR CNRS 6811, ENSAIA-INPL – Vandoeuvre-lès-Nancy, France
[3]Institute of macromolecular compounds, St-Petersburg, Russia

11.30-12.00 **Coffee break, Poster session**

CLOSING CEREMONY

12.00-13.00 **Farewell Address – Closing Remarks**

13.00-14.00 **Lunch**

19.00-22.00 **Farewell Dinner**

Saturday, May 12, 2012

08.00-09.00 **Breakfast**

10.00-13.00 **Excursion to Lassithi plateau**

13.00-14.00 **Lunch**

19.00-22.00 **Dinner**

Sunday, May 13, 20121

08.00-09.00 **Breakfast**

Departure of Participants

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Abstract Book

CYTOCHROME *C*- CARDIOLIPIN COMPLEX: A LIPOPROTEIN NANOSTRUCTURE THAT TURNS ON THE CASCADE OF REACTIONS TERMINATED BY SELF-DESTRUCTION OF LIVING CELLS

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There are two basic mechanisms of cell death of a living organism: death from the direct violations of the vital functions of cells (necrosis) and programmed death caused by distress signal, received from outside or inside the cells (apoptosis). In most cases, the lipid peroxidation(LPO) is the trigger of apoptosis. LPO reactions, in its turn, are catalyzed by the complex of cytochrome *c* (CytC) with anionic lipids, first of all, with cardiolipin (CL) abundant in inner mitochondrial membranes (Kagan, V.E., et al. NatureChem. Biol., 2005. 1: p. 223-232). Structure of Cyt-CL complex and the mechanism of its catalytic action were, however, a matter of discussion.
In our studies it was shown that Cyt-CL is a hydrophobic nanosphere with a diameter of about 11 nm and a cytochrome *c* in its center, completely covered with the polar heads of 30- 40 molecules of cardiolipin, whose tails form the outer layer of the sphere. The volume of CytC globule increases in the complex as compared to free cytochrome *c* in the aqueous phase; the natural conformation of CytC is disturbed, and the protein acquires a new property – the peroxidase activity.
The kinetics and mechanism of the peroxidase reaction catalyzed by Cyt-CL were studied by measurement and mathematical modeling of the kinetics of chemiluminescence in two systems:(1) Cyt-CL + H_2O_2 + luminol (substrate) and (2) Cyt-CL + hydroperoxide + unsaturated fatty acid (substrate) + coumarindye C-525 (the chemiluminescence enhancer). It was shown that Cyt-CL works like all other peroxidases, with the reaction circlebeing composed of, at least, 4 particular reactions. During the interaction of Cyt-CL with lipid hydroperoxides lipid radicals are found to be produced, which are thought to initiate chain lipid peroxidation. This reaction is crucial forCyt-CL lipoxygenase action, the first event in apoptosis development.
We investigated the regulation of Cyt-CL activity by chemical (antioxidants, nitric oxide) and physical (radiation of low power lasers) means. It was shown that antioxidants inhibited peroxidase action of Cyt-CL in micromolar concentrations. Nitric oxide blocked peroxidase activity due to binding by cytochrome *c* reaction center, while laser irradiation brought about the NO-CytC photolysis and restored the peroxidase activity.

ANTIVIRAL PEPTIDE NANOCOMPLEXES AS NOVEL THERAPEUTIC MODALITY

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HIV-1 and hepatitis C (HCV) co-infection became a leading cause of morbidity and mortality in current or former injection drug users and transfused hemophiliac patients. Both viruses use the similar routes for transmission, potentiate each other progression, complicate therapeutic application of antiretroviral drugs, due to liver toxicity, and interferon-based treatment for HCV, due to myelotoxicity, severe cognitive impairment and psychotic complications. As an additional potent therapeutic option for co-infected patients the peptides with specific broad anti-viral activities could be considered. However, *in vivo* application of these peptides is limited due to their rapid elimination, inactivation by proteases, and toxicity. To this end, incorporation of antiviral peptides into polyion complex micelles provides a valuable modality to minimize peptide degradation, increase the bioavailability and enable targeted delivery by shell modification. A structural cationic analog of amphiphatic α-helical peptide derived from the membrane anchor domain of the hepatitis C virus (HCV) NS5A protein with dual anti-HIV-1 and anti-HCV activity was incorporated into polyion complexes with anionic block copolymers of poly(ethylene glycol) (PEG) and polyanion. The resulting nanoparticles (APN) were ca. 30 nm in diameter at physiological salt concentrations, uniform (narrow size distribution) and had spherical morphology. Cellular uptake studies revealed accumulation of APNs in human macrophages in a time-dependent manner. APN retained antiviral activity as shown by pretreatment with APN in HIV-1 infected TZM cells and HCV infected Huh 7.5 cells which resulted in a decrease of HIV-1 and HCV reverse transcriptase activity. In vivo data demonstrated that APN are not toxic to animals and are able to suppress HIV viral replication.

RESORBABLE BIOCERAMICS FABRICATED FROM THERMOLYSED OCTACALCIUM PHOSPHATE (OCP)

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Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA) ceramics has long been regarded as a reference material for bone implants. Recently, research activity in this field is shifted toward calcium phosphates with a ratio of Ca/P less than that of hydroxyapatite, since they are more resorbable. We have proposed a route to fabricate biphasic ceramics $Ca_3(PO_4)_2/Ca_2P_2O_7$ from octacalcium phosphate (OCP, Ca/P ratio=1,33) as a precursor. A need for the precursor is dictated by the following reasons: (i) homogeneous distribution of the phases in the biphasic composite, (ii) low sin-

terability of the phosphate phases, especially calcium pyrophosphate ($Ca_2P_2O_7$, CPP).
The OCP powder was prepared by hydrolysis of $CaHPO_4 \cdot 2H_2O$ in a buffered solution. Prior to sintering, the powder of OCP was dehydrated at 450^{0}C, giving "OCP-450" precursor. Sintering of the "OCP-450" compacted samples was carried out at temperature 1100^0 C for 3 hours. Ceramic composites were evaluated for cytotoxicity and cell viability in fibroblast culture *in vitro,* and for bending strength (three-point bending test).
The as-received OCP powder consists of plate-like crystals having the so-called "apatitic" and of "hydrated" ("brushite") layers in their crystal structure. The structure of "OCP-450" precursor is somewhat similar to that of OCP, but looks less perfect and contains $P_2O_7^{4-}$-ions. HA and CPP as individual phases can be detected only during further dehydration at elevated temperatures. Thus, the structure of "OCP-450" represents HA-like layers and partially dehydrated "brushite" layers containing pyrophosphate anions. Thorough study of phase homogeneity of the ceramics fabricated from the "OCP-450" revealed rather uniform composition at the length scale of 50-100 nm (low-voltage EDX, BEI) apart from that one produced by mechanical mixing of CPP and tricalcium phosphate powders.
The ceramics fabricated from "OCP-450" reached 85% density and demonstrated high bending strength (up to 127 MPa). The reason underlying such a behavior is a very tight and ordered arrangement of lamellar particle during compaction (pressing) of the powder leading to rather dense and homogeneous ceramic structure. In vitro tests gave an evidence that the biphasic ceramics $Ca_3(PO_4)_2/Ca_2P_2O_7$ do not show any toxic effects with respect to fibroblast cells, and, therefore, has a good potential as a material for tissue engineering.
The work was supported by RFBR, grants # 10-03-00866, 11-03-12179-ofi-m-2011, 12-03-01025.

CELL-FREE PRODUCTION OF VOLTAGE-SENSING DOMAIN FROM HUMAN NAV1.4 CHANNEL FOR FUNCTIONAL AND STRUCTURAL STUDIES

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Eukaryotic voltage-gated Na^+ channels (Nav channels) represent the membrane receptors activated by the changes in the transmembrane potential and play the crucial role in the functioning of nervous, muscular and cardiovascular systems. Presently, in spite of a large fundamental and applied significance the aspects of Nav spatial organization and mechanisms of its voltage-gating and regulation remain little-studied. Alpha-subunit represents the main functional component of Nav channel; it encompasses 4 pseudo subunits surrounding an ion-conducting pore. Each pseudo subunit includes 6 transmembrane helices which compose voltage-sensing domain (VSD, helices S1-S4) and pore domain (helices S5-S6).
For functional and structural investigations of Nav channels and its domains the large-scale production systems are required. Recently the cell-free (CF) systems for expression of recombinant proteins attract much attention as a promising alternative to cell-based expression systems. In CF systems production of MPs in a soluble and folded form could be facilitated by the addition of membrane mimicking components e.g. detergent micelles, liposomes or lipid-protein nanodiscs directly into a reaction mixture. In the present work CF expression system was developed for production of VSD from human Nav1.4 channel. The protocols of VSD solubilization from the reaction mixture precipitate and domain incorporation into micelles, bicelles and lipid-protein nanodiscs were developed. NMR analysis of ^{15}N-labeled VSD in DPC micelles revealed the high level of isotope labeling. Developed CF expression system opens new perspectives for structure-functional studies of Nav channels. The data obtained as a result of these studies will find the application in the field of biotechnology and pharmacology.

EFFECT OF PLASMA H_2O_2 TREATMENT ON SURFACE PROPERTIES OF POLYHYDROXYALKANOATES

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Now actively developing a new direction of medical materials - cell and tissue engineering associated with the development of artificial organs.
The success of bioengineered scaffolds is largely determined by the properties of the material used to manufacture them. Polyhydroxyalkanoates (PHAs) have a special place among the actively developed biomaterials. They are regarded as one of the most promising materials for medical purposes, due to their unique set of properties necessary for tissue engineering (absolute biocompatibility, biodegradability, processability into various products). Surface properties of scaffolds play an important role for the attachment and proliferation. Products from PHA hydrophobic, and therefore to improve the adhesive properties of the surface of the scaffolds of these polymers, additional efforts are needed. One of the modern approaches used to modify the surface of the cellular matrix, is the handling of gas plasma. Plasma treatment of cell scaffolds of interest not only as a means of modifying the properties of their surfaces, but also as a sterilizing agent. The ratio of materials and products from them to the methods of sterilization is an important aspect of the success of their application.
This paper presents design methods of supporting different types of cell scaffolds of PHA, their structure, and the influence of plasma treatment on surface properties of H_2O_2 and the proliferative potential of adhered cells. The

experimental results showed that the sterilization of scaffolds in plasma H_2O_2 provides additional surface treatment, which promotes better adhesion and differentiation mouse fibroblast line NIH 3T3 on the surface of scaffolds.
Eukaryotic voltage-gated Na^+ channels (Nav channels) represent the membrane receptors activated by the changes in the transmembrane potential and play the crucial role in the functioning of nervous, muscular and cardiovascular systems. Presently, in spite of a large fundamental and applied significance the aspects of Nav spatial organization and mechanisms of its voltage-gating and regulation remain little-studied. Alpha-subunit represents the main functional component of Nav channel; it encompasses 4 pseudo subunits surrounding an ion-conducting pore. Each pseudo subunit includes 6 transmembrane helices which compose voltage-sensing domain (VSD, helices S1-S4) and pore domain (helices S5-S6).
For functional and structural investigations of Nav channels and its domains the large-scale production systems are required. Recently the cell-free (CF) systems for expression of recombinant proteins attract much attention as a promising alternative to cell-based expression systems. In CF systems production of MPs in a soluble and folded form could be facilitated by the addition of membrane mimicking components e.g. detergent micelles, liposomes or lipid-protein nanodiscs directly into a reaction mixture. In the present work CF expression system was developed for production of VSD from human Nav1.4 channel. The protocols of VSD solubilization from the reaction mixture precipitate and domain incorporation into micelles, bicelles and lipid-protein nanodiscs were developed. NMR analysis of ^{15}N-labeled VSD in DPC micelles revealed the high level of isotope labeling. Developed CF expression system opens new perspectives for structure-functional studies of Nav channels. The data obtained as a result of these studies will find the application in the field of biotechnology and pharmacology.

FEATURES OF BOTH STRUCTURE AND FUNCTIONING OF THE ENZYME LYSK ANTYSTAPHYKOCOCCAL BACTERIOLYTIC NANOZYMES

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At present, Staphylococcus aureus is one of the most dangerous pathogens of various diseases. About 90% of Staphylococcus aureus strains are resistant to one or more antibiotics. One of the most promising methods of staphylococcal infections treatment is the use of bacteriophage lytic enzymes. These enzymes are produced by the phages to destroy the peptidoglycan layer of bacteria. The enzyme LysK lyses cells of Staphylococcus aureus, including strains resistant to methicillin and vancomycin. LysK is not used in medicine due to its low stability at storage temperatures (4, 20-25°C) and temperature of action (37°C). Previously, it was found that LysK is inactivated by aggregation mechanism and usage of polycations is effective technique for LysK stabilization.
So, the aim of this study was to investigate the interaction of the enzyme LysK with the positively charged block copolymers of polyethylene glycol and polylysine ($EG_{114}Lys_{30}$ and $EG_{114}Lys_{10}$), polylysines 2.5, 9.6 and 55.2 kDa, polyarginines 5-15, 15-75 and > 70 kDa, an to determine optimal conditions for the stabilization of the LysK in the discussed temperature range.
Activities and stabilities of series of samples with different charge ratios polyelectrolyte/enzyme (from 1 to 100) and low molecular weight electrolyte concentrations (11, 300, 500 mM NaCl) at pH 9.0 and temperatures of 4, 22 and 37°C were investigated. Activities of samples were determined by turbidimetry. In all cases, the activity of LysK in mixtures with polymers is higher than (10 times) that of the enzyme without them.
It was shown that the addition of polymers to the enzyme leads to an increase in its stability under all temperatures in the presence of polylysines and their block copolymers with polyethylene glycol. Half inactivation time was chosen as quantitative parameter for characterization of the LysK stability. LysK half inactivation time was increased from 2 days to 2 months at 22°C by addition of polylysine with mass of 2.5 kDa and from 0.5 h to 100 h at 37°C in the presence of block copolymer $EG_{114}Lys_{10}$ in 300 mM NaCl.
By dynamic light scattering the formation of complexes between the enzyme and polylysines and PL-PEG block copolymers was detected, due to which, apparently, and the stabilizing effect is achieved. Hydrodynamic radius of polymer molecules corresponds to ~ 4 nm, the addition of the enzyme lead to its increase to 20-200 nm. These particles were named "bacteriolytic nanozymes".
By means of IR spectroscopy it was shown that that interactions of the LysK with polylysines and their block copolymers with polyethylene glycol lead to the structuring of the enzyme molecules, the proportion of alpha helices and beta structures increases and the content of disordered structures decreases. The presence of polyarginines causes destabilization and destructuring of the enzyme.
So, polylysines and their block copolymers with polyethylene glycol are effective additives for the LysK stabilization for using in medicine.
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CHITIN AND CHITOSAN NEW PROSPECTS AND OLD PROBLEMS

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Chitosan is a cation polysaccharide, possessing several benefits, as compared with synthetic polymers, namely – low toxicity, biocompatibility, biodegradation ability and availability. In this connection the growing interest to this natural biopolymer can be observed. The chitin/chitosan system has been thoroughly explored by scientists in its origin, composition, structure and physico-chemical properties. Chitosan is widely used in pharmaceutical and cosmetic industry, as well as in food, agricultural and some other industries. A potential standardization of the most common analyzing methods has been widely discussed during the past years but has not been tackled finally [S.A. Lopatin, M.S. Derbeneva, S.N. Kulikov, V.P. Varlamov, O.A. Shpigun.// J. Analyt. Chem., 2009, v. 64, 6, 648-651]. In the interlab study samples of chitosan were characterized with different methods for individual parameters. Over the world eleven scientific labs (including our Lab) were involved. The following parameters were analyzed: degree of deacetylation, viscosity, molecular weight, dry mater content, ash content, protein content, endotoxin content, microbial impurities, and heavy metal content [K. Richter.// EUCHIS'11, Abstracts of 10th Internat. Conf. of the European Chitin Society, May 20-24, 2011, p.4 (ISBN 978-5-4253-0134-5)].
Analysis of the special literature demonstrated that chitosan nanoparticles can be used predominantly as carriers for drug delivery, i.e. for delivery of biologically active substance into the target cells [A.A. Zubareva, A.V. Il'ina, A.N. Levov, V.S. Zueva, E.V. Svirshevskaya, V.P. Varlamov.// Progress on Chemistry and Application of Chitin and Its Derivatives, 2011, v. XVI, 61-70.]. Nanoparticles on the base of chitosan derivatives (N-acyl and succinoyl) meet all the requirements to such type of systems. Due to high density of the surface charge chitosan nanoparticles interact actively with cell membranes. These particles are biocompatible with living human tissues, because they don't cause allergic reactions as well as rejection; they biodegrade gradually to amino-sugars under specific enzyme action, and could be further digested completely in the living organism. They are not toxic, and easily eliminated from the organism, not causing side reactions. Chitosan nanoparticles, obtained in colloid form, are as a rule only partially stable due to self-aggregation. Lyophilization with the following resuspending in weak salt solutions didn't lead to nanoparticles with initial physico-chemical characteristics. The purpose of the present study consists in obtaining of stable nanoparticles on the base of chitosan-N-acyl- derivatives and succinoyl chitosan and receiving its complexes with proteins and drugs [A.V. Il'ina, N.M. Mestechkina, D.V. Kurek, A.N. Levov, P.I. Semenyuk, V.D. Scherbuchin, V.P. Varlamov.// Nanotechnologies in Russia, 2011, v.6, 1-2, 154-160. A.V. Il'ina, A.A. Zubareva, D.V. Kurek, A.N. Levov, V.P. Varlamov.// Nanotechnologies in Russia, 2012, v. 7, 1-2, 85-92.].

SEAWEEDS AND THEIR DERIVATIVES ARE AN INEXHAUSTIBLE SOURCE OF BIOPOLYMERS FOR BIOTECHNOLOGY DRUGS, FOOD SUPLEMENTS AND BIOLOGICALLY ACTIVE ADDITIVES

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Seaweed in connection with their unique chemical composition have long been used as a source of not only food, but also various biologically active substances and broad-spectrum biopolymers. The known food additives, such as alginates, carrageenans and agar are used for thickening andgelation of dairy, fish, meat and other food systems. Until now, the humanity has not yet invented a better row material than seaweed, for the production of these food additives. Furthermore, algal biopolymers are widely used in biotechnology, pharmaceuticals, as immobilization material of monoclonal antibodies, microorganisms, enzymes, etc. Many very important medications, for example insulin, have been received by a method of genetic engineering when using agarose gels. The gels of microbiological agar are used as a substratum at cultivation of antibiotics producers such as penicillin and streptomycin. In connection with the receiving of exhaustive data on the chemical composition of seaweeds and biological action of many their components nowadays is considered rational to use the polyfunctionality properties of mineral elements (Ca, Mg, K, I, Mo, Se, etc.), polysaccharides (alginates, laminarans, fucoidans) and low-molecular carbohydrates (mannitol) of brown algae in the technology of biologically active additives and some medications.To date, we have developed technology of integrated processing of Brown and red algae, which allows not only broad-spectrum nutritional supplements and biologically active additives (BAA), functional foods (FF) and substrates for the cultivation of microorganisms.

SYNTHESIZED NANO AND MICROFIBER MATRIX NETWORKS SUPPORT IMMUNOISOLATED PANCREATIC ISLETS FOR IMPLANTATION

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A novel method was developed to produce and incorporate a network of discrete, genipin-crosslinked gelatin nano

or microfibers around a pancreatic islet within a barium alginate microcapsule. This technique allows for the encapsulation of a porous extracellular protein-like matrix without the limitations of cellular aggregate seeding geometries that preclude their use in microparticles without diffusional limitations. Nanofibers were electrospun, and microfibers were produced from a newly developed vortex-drawn extrusion system with an alginate support matrix. Optimization of the extrusion methodology culminated in a hydrated fiber diameter of 22.3 ± 0.4 μm, a 98% reduction in cross sectional area, while making the process more reliable and less labour intensive. The optimized microfibers were encapsulated at 40 vol% within 294 ± 4 μm 1.6% barium alginate microparticles by an electrostatic-mediated dropwise extrusion system. Pancreatic islets extracted from Sprague Dawley rats were encapsulated within the microparticles, and analyzed over a 21-day study. Acridine orange and propidium iodide fluorescent viability staining and light microscopy indicated a significant increase in viability for the fiber-laden particles at days 7, 14, and 21, relative to fiber-free controls. The fiber-laden microcapsule system reduced the incidence of disrupted islet morphologies from 31% to 8% at day 21, and showed evidence of islet-fiber adhesion after only 1 hour of co-incubation and 24 hours of encapsulation. The novel microencapsulation method developed in this investigation could be developed into a modular scaffold system for tissue engineering beyond the field of islet research.

IN VITRO HEMOCOMPATIBILITY OF NANOCARRIERS TAILORED FOR BIOPHARMACEUTICAL DRUGS

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Abstract
The optimization of nanoparticles (NP) for drug delivery, in particular to target the BBB, imposes to verify their hemocompatibility both for toxicological and efficiency of targeting perspectives. Indeed the large surface they are able to expose to the biological environment promotes their interaction with various biochemicals, in particular proteins which can after adsorption elicit the activation of biological cascades either responsible from NP clearance or/and harmful body reaction (inflammatory / coagulation).
In the frame of the European Integrated Project : "Nanobiopharmaceutics", we have the opportunity to compare the hemoreactivity of about 145 different NP samples differing in core and surface chemistry and classified according to their expected difference in hydrophobicity based on the nature of their core materials. According to this classification, PLGA nanoparticles, polyglycidol-polyethyethylene oxide nanoparticles, polyglycidol thyolated or polyacrylamide nanogels, and polyelectrolyte complexes either based on polyamidoamine or poly(N,N-dimethylamino-2-ethylmethacrylate) have been evaluated within a concentration ranging from 0.3 to 1000 μg/mL. These in vitro tests have been realized for screening purpose adopting normal human bloods and according to Iso 10993.
As a summary of this extensive study, our results clearly highlight that most of the polymeric nanoparticles evaluated give rise to some alterations of the blood components. In particular the platelets, intrinsic pathway of coagulation and complement activation are the most reactive biological parameters in the presence of these nanostuctures.
Although not strictly related to the surface chemistry our classification has also allowed us to derive some clear correlations between nanomaterial properties and their hemoreactivity.
Within the class of polyelectrolyte electrolyte complexes, the modifications brought in the surface chemistry has drastically improved their hemoreactivity.

Keywords
Nanoparticles, blood brain barrier, biopharmaceutical drugs, hemocompatibility, hemoreactivity, complement activation.
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"SMART" POLYMERS FOR NUCLEAR MEDICINE

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With increasing number of oncological diseases new methods have been searched for and researched to take cancer over control. The most investigated methods in this area are the radionuclide diagnostics and therapy.
An important task of nuclear medicine is to achieve maximum tumor destruction with minimal damage to the surrounding normal tissues.
This problem can be solved through development of the radiopharmaceuticals with a radionuclide bound to the polymer molecule that has a thermotropic transition at the temperature of the human body. In this case radioactive isotopes will be localized in the vicinity of the tumor.
The most promising biocompatible thermo-sensitive polymers for developing self-collapsing therapeutic radiopharmaceuticals include associating polyelectrolytes on the basis of N-isopropylacrylamide (PNIPA) and N-vinyl-

caprolactam (PVCL) copolymers with a thermotropic transition below 36 °C.
The main objective of this work is to develop a polymer-containing radiopharmaceutical for thermally-stimulated localization of radionuclides in the vicinity of the tumor.
We suggest that the mobility of radioactive isotopes in the vicinity of the tumor should be limited in two ways.
The first way implies the research of the radiopharmaceutical based on two-component interpolymer complexes of PVCL and iodocasein protein. The dominating features of the drug are divided component-wise between heat-sensitive PVCL polymer and iodocasein protein containing amino acid residue – tyrosine with a phenyl ring covalently bound to iodine-131.
Thermodynamic and hydrodynamic properties of individual co-components and polymer-protein complexes were studied by the methods of viscosimetry and dynamic light scattering. The synthesized samples of PVCL and PVCL-M had molecular mass of $46x10^3$ and $1.2x10^6$, respectively. It was observed that at the temperatures below thermotropic transition the main contribution to the dynamic light scattering of aqueous PVCL solutions is made by polymer coils with an average hydrodynamic radius of 6 nm for PVCL-N and 51 nm for PVCL-M. At 40 °C a group of single coils in a dilute solution of both samples was transformed into the group of polymer clusters with a hydrodynamic radius of 400±20 nm independent of PVCL molecular weight.
Based on viscoelastic properties of the drug precursor determined before and after thermotropic transition in the medium of blood serum, optimal compositions were selected on the basis of PVCL-M suitable for preparing a self-collapsing radiopharmaceutical.
Radiopharmaceutical solutions with 1.3 MBq/ml volume activity were prepared for model experiments on laboratory animals. The studies in mice with Ehrlich carcinoma showed a high level of drug concentration in the tumor after intratumoral injection, which was maintained for 7 days. This time is sufficient to achieve a therapeutic absorbed dose of internal irradiation. The study of acute toxicity after intraperitoneal and subcutaneous administration showed that the drug has no toxic effect. The results indicate that this radiopharmaceutical can be used successfully in the radionuclide therapy of solid tumors.
The second method of radiopharmaceutical development implies direct bonding of the radionuclide with a chain of the macromolecule based on PNIPA. To do this, NIPA copolymers were synthesized with glycidyl or benzyl esters of methacrylic acid, which reacted with complexons (diethylenetriaminopentaacetic and diethylene triaminopentamethylephosphonic acid). These complexons form strong chelate bonds with polyvalent metal cations, such as samarium-153, rhenium-188, yttrium-90. Therefore, radiopharmaceuticals can undergo a phase transition near the temperature of the human body, and effectively bind and fix various polyvalent radioactive ions of transition metals.

TUMOUR-TARGETED POLYMER CARRIERS BASED ON STAR HPMA COPOLYMERS PREPARED BY RAFT POLYMERISATION

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Drug delivery systems enabling controlled drug release have been intensively studied during last few decades. One of these systems - water-soluble polymer conjugates of antitumour agents is in the spotlight.
Conjugates of anticancer drug doxorubicin (Dox) with copolymers based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) facilitating tumour targeting and pH-controlled intracellular drug activation exhibited high antitumour activity against various tumour models (*e.g.* EL4 mouse lymphoma) *in vivo*. It was found that molecular weight of the polymer-drug conjugates strongly influenced their anti-tumour efficacy; high-molecular-weight (HMW) nanotherapeutics were effectively accumulated in solid tumours due to the enhanced permeability and retention (EPR) effect. The HMW star-like HPMA-based conjugates with Dox, paclitaxel or docetaxel showed superior activity in the treatment of solid tumors in mice. Unfortunately, their molecular weight distribution was too broad and their structure less defined, because they were prepared using free radical polymerisation.
In this contribution, we present improved synthesis and physico-chemical properties of novel star polymer-Dox conjugates based on well-defined polymer precursors synthesised by controlled radical Reversible Addition-Fragmentation chain Transfer (RAFT) polymerisation. This technique provides polymers with narrow molecular weight distribution and one polymer-end functional group. HMW polymer carriers were synthesised by grafting of the semitelechelic polymer precursors on polyamidoamine (PAMAM) dendrimers which resulted in a star structure with dendritic core and HPMA copolymers forming arms. Polymer precursors contained Boc-protected hydrazide groups, which enabled, after deprotection, attachment of Dox by pH-sensitive hydrazone bond. While molecular weight of polymer precursors was about $3{\cdot}10^4$ and the star HMW conjugates $1{\cdot}10^5$ – $3{\cdot}10^5$, polydispersity of all polymer conjugates remain very low (1.1).
The conjugates exhibited pH-controlled drug release. While the hydrazone bond was relatively stable in a buffer at neutral pH modeling conditions during transport in blood circulation (up to 10% released Dox/24 h), Dox was released under mild acidic conditions imitating intracellular environment typical for endosomes of tumour cells (about 85% Dox released in24h at pH 5.0).
The novel star polymer-drug conjugates fulfil all necessary requirements for effective nanotherapeutics thus forming a new class of drug delivery systems with highly defined structure and high efficiency in the treatment of solid

tumours.
Acknowledgements
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SYNTHESIS OF WELL-DEFINED SEMITELECHELIC *N*-(2-HYDROXYPROPYL)-METHACRYLAMIDE POLYMERS BY RAFT POLYMERIZATION

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The water-soluble polymers are intensively studied as potential nanocarriers of biologically active compounds in drug delivery field. The final biological activity of polymer drug/protein conjugates is significantly influenced by the molecular weight, polydispersity and architecture of the polymer nanocarrier.
The reversible addition fragmentation chain transfer (RAFT) polymerization enables preparation of the broad range of polymers, statistical and block copolymers, and semitelechelic and telechelic polymers with well-defined molecular weight and low polydispersity.
Here we are focusing on the synthesis of semitelechelic polymers based on *N*-(2-hydroxypropyl)methacrylamide (PHPMA) and quantitative analysis of the effect of azo initiators on the structure of α-polymer chain ends in RAFT polymerization. Series of azo initiators (INI) based on 4,4′-azobis(4-cyanopentanoic acid) and 4-cyano-4-(thiobenzoylthio)- pentanoic acid chain transfer agents (CTA) containing different functional groups (azide, propargyl, thiazolidin-2-thione, pyridyldisulfide, -NH-Boc and –NHNH-Boc) were synthesized and used for the synthesis of semitelechelic PHPMA by RAFT. Influence of the azo initiator on the structure and functionality of α-polymer chain ends was studied on the semitelechelic PHPMA prepared by RAFT polymerization initiated with 4,4′-azobis(4-cyanopentanoyl-valine or leucine methyl ester) (INI-Val or INI-Leu) in the presence of 4-cyano-4-(thiobenzoylthio)pentanoyl-alanine methyl ester (CTA-Ala) as chain transfer agent. Amino acid analysis enabled determination of the ratio of amino acids Val/Ala or Leu/Ala incorporated into the α-polymer chain end which gave direct information on the role of both components of the initiation system controlling the structure and functionality of the final polymer. The results clearly show that with increasing ratio of CTA/INI in polymerization mixture both, the content of Val or Leu from initiator in the α-polymer chain end and yield of polymerization, decrease.
The incorporation of Val amino acid from initiator into α-polymer chain end increases with polymerization time and temperature at constant monomer/CTA/INI ratio. The addition of radical from the INI-Val to CTA-Ala and following fragmentation resulting in formation of a CTA-Val in polymerization mixture was proved by HPLC and mass spectroscopy.
The change of ratio of monomer/CTA at constant ratio of CTA/INI and polymerization time doesn't influence the structure of α-polymer chain end.
Obtained data demonstrate that semitelechelic polymers with well-defined structure and uniform functionality of the α-polymer chain end can be only prepared by RAFT polymerization if the INI and CTA with the same functional groups are used. These polymers were used for the synthesis of polymer protein conjugates.
This work was supported by the GA AS CR (grant No. IAAX00500803) and GA CR (grant
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COMPARATIVE STUDY OF WIDE TAXONOMIC NATURAL CORALS FOR BONE TISSUE RECONSTRUCTION AND ENGINEERING

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Aim of study. Comparative estimation of physicochemical properties, acute cytotoxicity, cell matrix surface properties, biocompatibility and osteoconductive potencies of wide taxonomic NC skeleton for bone tissue defects reconstruction and engineering.
Materials and methods. Collection of corals (2 classes of Coelenterata (Anthozoa, Hydrozoa), 10 families and 23 species) was chosen: Oculinidae (1 sp.), Caryophyllidae (1 sp.), Acroporidae (8 sp.), Fungiidae (1 sp.), Faciidae (1 sp.), Pocilloporidae (8 sp.), Agariciidae (1 sp.), Merulinidae (1 sp.), Helioporidae (1 sp.) and Milleporidae (1 sp.). For physicochemical NC characteristics estimation the X-ray and spectral analysis, infrared spectroscopy, scanning electronic microscopy were made; the kinetic of bioresorption was studied. In vitro experiments by MTT-test the acute cytotoxicity (24 hours of cultivation) and matrix characteristics of NC surface (3, 7, 10 and 14 days) were studied and in vivo – biocompatibility (model of subcutaneous NC implantation, mice; 2, 4, 8 and 12 weeks) and osteoconductive potencies (model of marginal excision; Wistar rats; observation times 3, 6, 9 and 12 weeks).
Results. All NC specimens was shown to consist of calcite ($CaCO_3$), but their crystalline grid have some differences (isomorphic aragonite substitutions were observed). NC specimens differs by dashes of transition metals, concentrations of which do not exceed maximum permissible. These specimens of NC are non-toxic (with the exception

of Heliopora coerulea), have a porosity 50-60% with pore size about 500-2000 μm and developed surface with marked matrix properties. Cells actively fasten and proliferate on corals, effectively colonize all surface, including pores space. These specimens of NC was shown to resorbe both in model liquids and during of subcutaneous and intraosteal implantation. In process of biodegradation the deposition of apatite layer is observed, that contributes qualitative osteointegration of implant with bone. The rate of these specimens biodegradation was approximately equal in model experiments. All NC corals are biocompatible and have expressed osteoconductive properties. They not only carry out frame function, but integrate in bone and promote active revascularization and migration of osteogenic cells. Additionally to all, these NC specimens were 3D matrix for MMSC and significantly reduced time of bone defect reparation.

TARGETED POLYMER THERAPEUTICS WITH A COILED COIL MOTIF

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Polymer antitumor therapeutics exhibit several advantages compared with low-molecular-weight drugs. They offer prolonged blood circulation, improved accumulation in solid tumors and possible targeting with a tumor-specific ligand which is very often an antibody or its fragment. We have developed a new way of attachment of targeting recombinant antibody fragments to polymer drug carriers using heterodimeric coiled coil peptides.
We have synthesized and characterized a new class of targeted water-soluble polymer cancerostatics based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers and recombinant single chain antibody fragments (scFv). The copolymers consist of anti-cancer drug doxorubicin (Dox) bound via an enzymatically cleavable GFLG tetrapeptide spacer and peptide sequence $(VAALEKE)_4$ (peptide E). The conjugate is targeted to murine leukemia BCL1 cells with recombinant scFv fragment of B1 antibody (Ab) containing peptide sequence $(VAALKEK)_4$ (peptide K). Peptide K forms a stable non-covalent coiled coil heterodimer with peptide E. Azidopentanoyl derivative of peptide E was attached to the polymer carrier containing propargyl group via azide-alkyne cycloaddition - "click chemistry" - catalyzed with complex of Ru(II) (pentamethylcyclopentadienyl (cyclooctadiene) ruthenium(II) chloride). Both cell binding and cytotoxicity of the targeted polymer complexes were tested *in vitro* using two cancer cell lines – BCL 1 as a positive cell line for B1 monoclonal antibody and 38C13 as a negative control. The presence of targeting ligand in the conjugate increased both the cytotoxicity and cell binding more than 100 times (compared with the non-targeted polymer-Dox conjugate) if incubated with the BCL 1 cells. No differences in cell binding and cytotoxicity between the targeted and non-targeted conjugates were observed using the negative control cell line 38C13. The presented method offers a universal non-destructive method of preparation of well-defined polymer-protein conjugates. Consequently, the method might facilitate obtaining of eventual regulatory approval for this clinical testing of new class of nanomedicines.
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BIODEGRADABLE PHAS: PRODUCTION, BIOMEDICAL INVESTIGATIONS, APPLICATIONS

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The work presents the results of biomedical investigations and applications of resorbable linear polyethers - polyhydroxyalkanoates (PHA). The registered trade mark of material and products - Bioplastotan™.
We investigated highly purified PHA samples produced at the Institute of Biophysics SB RAS and synthesized by bacteria Ralstonia eutropha B5786 using the technology that allows to obtain PHAs having various chemical structures and high degree of purity, applicable for medical purposes, including contact with blood. Using PHAs in various phase states (solutions, emulsions, powders) we produced and investigated the structure and properties of two- and three-dimensional matrices in the form of flexible transparent films, membranes, superfine fibers, microparticles, sponges, three-dimensional solid and porous constructions. We demonstrated the possibility of application of conventional methods for sterilization of matrices without changing of the structure, loss of strength and deterioration of surface adhesion properties. With the help of microscopy, detection of protein synthesis and DNA by the cultivated cells, MMT test, it was shown that in the cultures of fibroblasts, hepatocytes, endothelium cells and osteoblasts PHA-matrices haven't cytotoxicity at direct contact with any of the investigated cells and that the cells can be cultivated in vitro.
Gel-spun technology and melt extrusion were used to produce solid monofilaments which were proved to be suitable for closure of musculo-fascial wounds and in abdominal reconstructive surgery of bowels and bile passages.
We constructed three-dimensional solid and porous bone-replacing implants from polyhydroxybutyrate/ hydroxyapatite (PHB/HA) composite with various content of components. Using the primary culture of osteoblasts ob-

tained from mesenchymal stromal cells of bone marrow we showed that the composite is biocompatible and can be used as matrix for in vitro cultivation of osteoblastic cells.
Now we have an experience of successful clinical application of experimental medical wares made of BioplastotanTM. We demonstrated the efficiency of application of polymer barrier membranes and granular material in maxillofacial surgery for directed regeneration of jaw-bone defects and suitability of flexible membranes in arthroplasty as a hyaline cartilage protector, for prevention of intraarticular adhesive processes leading to anchylosis in hemophiliacs.
The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and Program of the President of Russia for young Doctors of Sciences (Grant No MD-3112.2012.4).

LABELING OF BIOLOGICALLY ACTIVE POLYMER (POLY-N-VINYLPYRROLYDONE) DERIVATIVES WITH "COLD" Re AND "HOT" ^{99m}Tc AND ^{161}Tb.

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Biologically active synthetic polymers (BASP) are widely applied for targeted delivery of diagnostic or therapeutic agents to diseased sites in the human body. They are generally inexpensive, can be readily functionalized and conjugated with cargo molecules. Additional advantages of BASP comprise high drug loading capacity and chemical flexibility for modifications. Synthetic polymers are especially useful as carrier molecules for the delivery of anticancer compounds due to the ability to accumulate in tumour tissue as a result of well-known EPR effect. The efficiency and selectivity of antitumor action can be enhanced by the attachment to polymer carrier peptides or other ligands specificity interacting with receptors localized on the surface of cancer cells.
The presented study describes the design of tumour specific BASP conjugates for targeted delivery of radiopharmaceutical and imaging agents to cancer cells. Polymer carriers of N-vinyl-amide class are relatively easy in preparation, well studied and can be modified by the desired chelating moiety and low molecular tumour-specific vectors such as [D-Lys^6]-GnRH or related peptides. In the frame of this study special attention was paid for choosing of radiometal with appropriate emitting characteristics – ^{99m}Tc(for diagnostics) and ^{161}Tb (both for diagnostics and therapy).
By using oxime ligation technique polyvinylpyrrolidone (PVP) derivatives containing DOTA chelating groups and pyruvic acid residues were efficiently conjugated with highly active luliberin analogue – [D-Lys^6]-GnRH, modified by aminooxyacetic acid. Polymer complexes with "cold" $Tc(CO)_3$ and Tb spices were prepared and characterized by NMR, UV, IR, ESI-MS, viscometry and dynamic light scattering techniques. Special attention was paid for the design of appropriate conditions for the verification of their radiochemical purity using analytical chromatography.
Ultrashort CIM (Convective Interaction Media) columns appeared to be most effective for the fast separation of low molecular components from macromolecules (the time of analysis is 5 min) and determination of molecular mass characteristics of metallo-polymeric conjugates.
Radiolabeling experiments were performed using standard protocol (70°C, 15 min – 24 hr, pH 4-5). The radiochemical yields were 90% for $^{99m}Tc(CO)_3$(PVP-DOTA-[D-Lys(AOA)^6]-GnRH) and almost quantitative for ^{161}Tb(PVP-DOTA-[D-Lys(AOA)^6]-GnRH). Both conjugates were stable in human plasma for 24 hr.
Presented results illustrate the efficiency of oxime ligation technique for the design of polymer carriers for the targeted delivery of radiopharmaceutical agents to cancer cells.
This work was supported by SCOPES Project No. IZ73Z0 and RFBR

STRUCTURE AND MECHANICAL PROPERTIES OF ULTRAFINE GRAINED TITANUM PRODUCED BY THE SEVERE PLASTIC DEFORMATION AND ITS MEDICAL APPLICATION

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One of the ways to increase mechanical properties of metals is formation of ultrafine-grained or nanostructured state in the bulk by severe plastic deformation. At present a set of the severe plastic deformation methods has been developed. There are many experimental data illustrating a great improvement of mechanical characteristics, such as limit strength, yield strength, fatigue strength, wear resistance, microhardness and so on as a result of the severe plastic deformation.
Today, a combined method of severe plastic deformation, comprising abc-pressing in a press-mold and multiple rolling, to produce the billets of technically pure titanium VT1-0 in nanostructured / ultrafine-grained state, is used in ISPMS of SB RAS. This method represents multiple uniaxial pressing of coarse-grained titanium billets in a press-mold with the change in deformation axis under each new cycle of deformation and a successive step-by-step de-

crease of temperature from 700°C to 400°C, then - multiple rolling in the grooved rollers and pre-recrystalline annealing at the temperature of 300-350°C. This severe plastic deformation method allows us to produce titanium rods in nanostructured / ultrafine-grained state with a homogenous structure in the bulk of the billet and with the average size of the elements of the grain-subgrain structure (grains, subgrains, fragments) of 100 nm and less. Mechanical properties (yield point, ultimate stress, hardness and fatigue strength) of the nanostructured titanium, produced by the method, amount to those of medium-strength titanium alloys, i.e. Ti-6Al-4V. The nanostructured titanium remains the stable microstructure and properties in the temperature interval from a room temperature up to 300°C.
The modern constructions of intraosseal screw dental implants of different modifications from the VT1-0 nanostructured / ultrafine-grained titanium (they are characterized by the increased osseointegration) have been developed. Instruments and implements necessary to perform surgical and orthopedic procedures with dental implants have been developed.
The clinical tests of nanostructured titanium dental implants have been completed. They have confirmed that the implant constructions correspond to the modern state of implantology and their usage do not trigger any complications at the surgical and orthopedic stages of the treatment.

POROUS BIORESORBABLE CERAMICS BASED ON CALCIUM PYROPHOSHATE AND POLYPHOSPHATES

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Introduction
The growing demands of regenerative medicine and orthopedic surgery require new bioactive materials for bone implants. Particular attention is paid to composite materials containing bioresorbable phase. Being the active source of necessary elements for inorganic part of bone resorbable materials are replaced by native growing bone tissue in the organism. Calcium-deficient or carbonate-containing hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$, amorphous calcium phosphate, tricalcium phosphate (TCP) $Ca_3(PO_4)_2$, phosphate glass, calcium pyrophosphate (CPP) $Ca_2P_2O_7$, calcium polyphosphates, renanite $NaCaPO_4$ can be regarded as such phases.
Materials and methods
The aim of this work is to obtain porous resorbable ceramic material based on calcium pyrophosphate $Ca_2P_2O_7$ and polyphosphates. First, initial samples for ceramics were prepared by forming from cement mass. Then they were annealed at temperature range 600-1000°C. Brushite cements were synthetized from β-TCP and orthophosphoric acid by reaction (1):
$Ca_3(PO_4)_2 + H_3PO_4 + 6H_2O = 3CaHPO_4{*}2H_2O$ (1),
In order to control the setting time of cement mass sodium pyrophosphate $Na_4P_2O_7$, sodium hexametaphosphate $(NaPO_3)_6$ and citric acid were added to the liquid before mixing with TCP powder.
During the heat treatment brushite converts to CPP by reaction (2):
$CaHPO_4{*}2H_2O \rightarrow CaHPO_4 \rightarrow Ca_2P_2O_7$ (2),
System of sodium salts $(NaPO_3)_6$ and $Na_4P_2O_7$ has a relatively low melting point. The presence of the melt promotes liquid sintering at rather low temperatures and improves the mechanical characteristics of ceramic materials. Porous structure (about 70% porosity with pore diameter ≈100 μm) is promoted by gas release during heat treatment of the cements.
According to XRD-analysis, final ceramic material is based on CPP and contains 5-10% of double polyphosphates of sodium and calcium.
In vitro and *in vivo* tests demonstrated that our material is nontoxic, bioactive and resorbable.
Conclusions
Thus, in this study bioactive ceramic material based on CPP and polyphosphates with high rate of resorption and porous structure was obtained.

T1-CONTRAST AGENT BASED ON MONOCLONAL ANTIBODY FOR MRI VISUALIZATION OF TUMOR CELLS OF GLIOMA

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Introduction
Human glioblastoma multiforme is the most aggressive form of brain tumors with high mortality and extremely poor prognosis. It is important to visualize borders of glioma at an early stage. One of the strategies is conjugation of contrast agents with monoclonal antibodies (mAb) to targeting proteins, such as receptors of vascular endothelial

growth factor (VEGF) or integral membrane protein connexin 43 (Cx43), which are overexpressed in tumor periphery. The goal of this study was to develop the targeted T1-contrast agent based on specific mAb for visualization of tumor cells of glioma C6.

Methods

Polylysine (PLL) was modifie**d with diethylenetriaminepentaacetic acid (DTPA)**, loaded with Gd(III) ions and then conjugated with mAb Cx43 or mAb VEGF (PLDGd-mAb). Immunofluorescent analysis of fluorescein-labeled contrast agents was performed on live cells of glioma C6, using non-specific PLDGd-IgG as a control. Cytotoxicity of conjugates was analyzed by MTT-test (glioma C6, HEK293 cells). T1-relaxivity and MRI studies were performed on 7T MR-tomograph ClinScan (Bruker). Signal intensity of specific and non-specific T1-agents (0,03mmol Gd/kg**)** after i.v. injection were monitored (5,10,30min and 1,24h).

Results

Immunofluorescent analysis of specific T1-contrast agent (Figure 1A) revealed higher affinity to C6 cells compare to non-specific agent (Figure 1B). Maximal non-toxic concentration of contrast agents was 0,5mg/ml. Obtained T1-agents had higher relaxivity value (6,9$mM^{-1}s^{-1}$) compare to commercial agent Magnevist (4,4$mM^{-1}s^{-1}$). MRI study showed that specific T1-agents had greater signal enhancements than non-specific conjugate or than Magnevist (Figure 2) in glioma C6 *in vivo.*

Summary

Taken together these data confirm that obtained T1-contrast agents have high relaxivity and high affinity to glioma cells *in vitro* and *in vivo.*

Investigations were supported by Russian Ministry of Science and Education (grant No11.G34.31.0004)

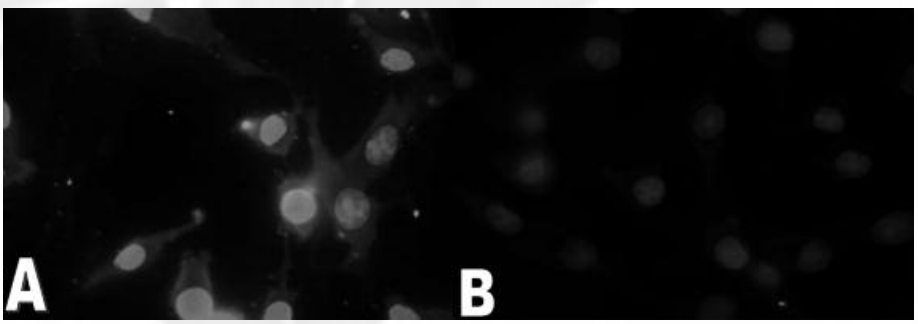

Figure 1. Immunofluorescent analysis of fluorescein-labeled specific PLDGd-Mab **(A)** and non-specific PLDGg-IgG **(B)** agents.

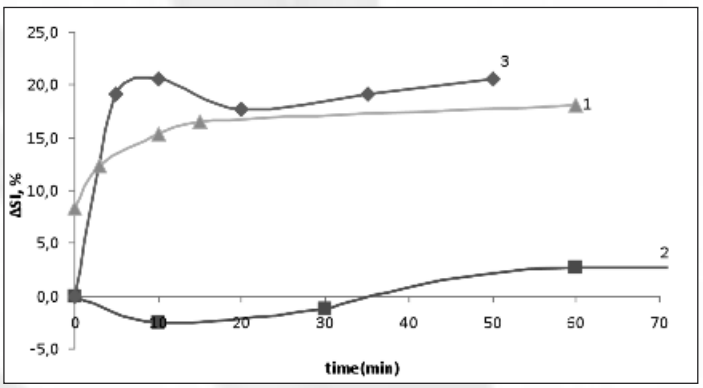

Figure 2. Plot of the signal intensity of glioma obtained from contrast-enhanced dynamic MRI of rats at dose 0,03mmolGd/kg specific conjugates **(1)** and non-specific conjugates **(2)** or 0,1mmolGd/kg Magnevist **(3)**.

SURFACE MODIFICATION OF POLYMERIC BIOMATERIALS BY LOW-TEMPERATURE PLASMA TO CONTROL CELL AFFINITY

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The primary interactions between biological tissues and biomaterial surface include several phenomena, such as hydration, adsorption of molecules from extracellular liquid and dissolution of atomic, ionic or molecular fragments from the biomaterial. These processes are followed by cell adhesion, spreading, growth and roliferation. In this regard, scaffold design in tissue engineering is rather difficult challenge which includes study of bulk physicochemi-

cal properties of the material used as well as evaluation of interfaces with well defined surface chemistry and topography capable to promote cell growth and proliferation. Low-temperature plasma surface modification is a powerful tool to vary biomaterial surface properties, chemical structure, and thus to control cell affinity of the scaffolds for tissue engineering.
This research deals with the study of low-temperature DC-discharge plasma treatment (working gas - air, 50 mA, 60 sec) effect on the surface properties of films prepared from natural (chitosan, gelatin), synthetic (poly(L,L-lactide), PLLA) polymers and composite materials on their base.
Film samples were prepared by solvent casting from 5 wt-% solutions of the initial polymers, namely chitosan (60 and 300 kDa), gelatin and PLLA (160 kDa) whereas composite films were fabricated from a colloidal solution of a ternary blend of chitosan, gelatin and PLLA obtained by solid-state reactive blending (SSRB). The obtained films were treated with air DC discharge plasma and the effect of plasma modification was studied by contact angle and surface charge measurements, XPS and SEM. The ability of the films to support growth of animal cells was tested using mouse fibroblasts (L929) as a model cell line.
Plasma modification of the polymer films resulted in a substantial increase in fibroblasts viability on the plasma treated synthetic PLLA films and to a rather strong decrease of cell growth on the plasma treated chitosan and composite ones. A significant difference in cell behaviour on the plasma-modified films in comparison with non-treated ones was explained by superposition of morphological factors on changes in surface chemical structure and charge. Thus, film surface modification with air plasma could be proposed as a good tool to control cell affinity to the polymer surface.

GLIOMA C6 VISUALIZATION BY MRI WITH CONJUGATE OF MAGNETIC IRON OXIDE NANOPARTICLES AND MONOCLONAL ANTIBODIES TO VEGF.

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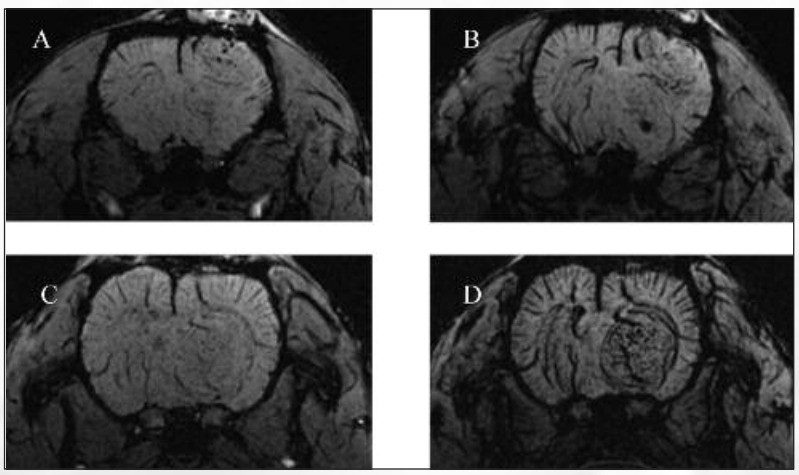
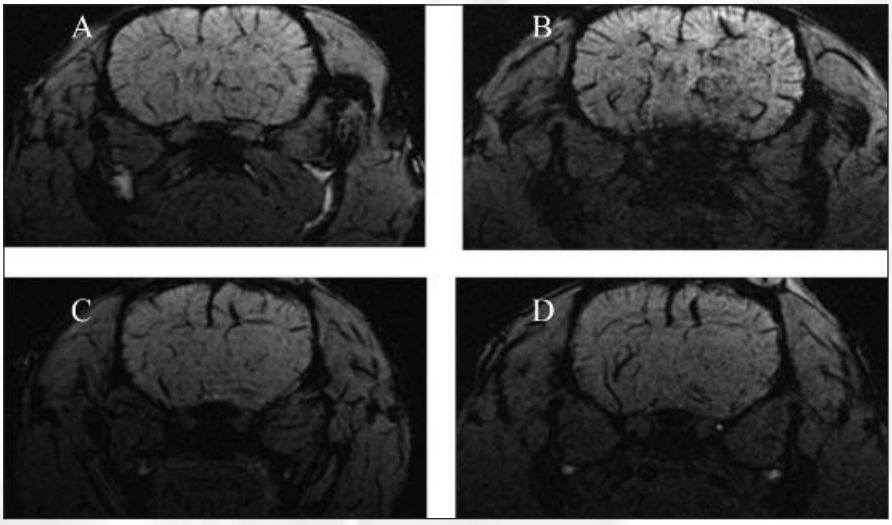
Purpose
The aim of the study was to obtain stable water colloidal solution of iron oxide nanoparticles, coated with BSA, investigate their physical and chemical properties and show their efficiency as tumor contrasting agent for MRI.
Methods and results.
Synthesis of nanoparticles was made from iron (III) acetilacetomate. The size of obtained nanocrystalls was determined by TEM was 12±3 nm. As biodegradable coating agent bovine serum albumin were used. Size and ζ-potential of nanoparticles were 95nm and 45 mV respectively. MTT-assay showed no significant cytotoxicity on cell cultures at concentrations of iron up to 1 mg/ml. T2-relaxivity of obtained colloidal solutions was 4500 ml/(mg/s^{-1}). BSA coated nanoparticles were conjugated with an antibodies to VEGF. Specific interactions of vectorized nanoparticles with glioma C6 cells were shown. MRI study of rat brain with experimental glioma after i/v injection showed accumulation in tumor vasculature in comparison with commercial analog (Picture 1). MRI study after 24 hours after injection showed higher accumulation of nanoparticles labeled with monoclonal antibodies to VEGF (MAb-VEGF) then nanoparticles conjugated with non-specific mouse IgG (Picture 2).
Summary
Taken together these data confirm that biocompatible iron oxide nanoparticles, with low cytotoxicity, and high affinity to brain tumor cells suitable as an MRI contrast agent were obtained.



Picture 1. Rat brain MR- images before (A,C) and 20 minutes after intravenous injection of Ferridex (B) and BSA coated nanoparticles conjugated with MAb-VEGF (D).



Picture 2. Rat brain MR- images before (A, C) and 24 hours after intravenous injection of BSA nanoparticles conjugated with nonspecific mouse IgG (D) with MAbVEGF (B).

Investigations were supported by Russian Ministry of Science and Education (grant No11.G34.31.0004), and grant NIH COBRE 1P20RR021937.

APPLICATION OF MANUFACTURING NANOPARTICLES FOR THE DETECTION OF BIOLOGICALLY ACTIVE COMPOUNDS

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Nanoparticles with different properties (colored, fluorescent, magnetic, conductive etc.) are applied widely in immunochemical test-systems for labeling, separation or concentration of immune compounds. The report presents a comparative analysis of nanoparticles from different classes and their complexes with antibodies in terms of their opportunities for analytical purposes. Knowledge of the structure–property relationship for nanoparticle–protein conjugates allows one to change their composition for the directed regulation of functional characteristics.
On the example of colloidal gold (CG) the relationship between antibodies immobilization on surface of nanoparticles with different size, effective value of antigen-antibody binding constant and analytical characteristics of the test-systems is considered. It is found that increase of CG diameter from 6 to 33 nm causes 27-fold growth of sensitivity for immunochromatographic detection of viruses. Examples of cascade systems for signal enhancing with the use of nanoparticles are given. On the example of mycotoxins detection parameters of immunochromatographic and immunosensoric assays are compared for the cases of specific and anti-species antibodies labeling by CG. The use of CG conjugate with anti-species antibodies provides 10-fold decrease of the limit of detection. The application of video-digital detectors for grounded choice of optimal reactants ratio in immunochromatographic test-systems and quantitative registration of the assay results are characterized. Benefits and limitations of CG and other labels for immunochromatography are estimated. On the examples of antibiotic chloramphenicol and allergen-specific antibodies the efficiency of the application of antibody conjugates with water-soluble semiconductor quantum dots (QD) on the basis of CdSe/ZnS is demonstrated. Magnetic ultradisperse immunocarriers on the basis of mixed oxide of iron are characterized as tools to decrease the limit of detection of immunoenzyme assay; their effectiveness in combination with different systems of detection is estimated.
The results of the development of immunochromatographic test-systems with the use of nanoparticles for express detection of antibiotics, drugs of abuse, viral and bacterial antigens, specific antibodies against infectious agents are given. Promising ways of bioassay development on the basis of nanoparticles application for further improvement of methods for medical diagnostics are finally considered.
This work was supported by the Ministry of Education and Science of the Russian Federation (state contract # 02.740.11.0868, June 28, 2010) and the Program of Basic Research of the Presidium of Russian Acad. Sci. # 8.

NEW POSSIBLE IMMUNOLOGICAL MARKERS IN DIAGNOSTICS OF ADDICTIVE STATES: DRUG ADDICTION, ALCOHOLISM, PATHOLOGIC GAMBLING

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In resent 15-20 years new research immunology branch was formed; it deals with the role of natural antibodies (N-Ab) investigation in course of biochemical processes in human organism. N-Ab against endogenous bioregulators

(EB) - neuropeptides and biogenic amines - exist in blood of healthy people. These molecules are able to bind corresponding bioregulators and so to participate in homeostasis regulation. Our earlier fundamental investigations allowed establishing new data about N-Ab. Specific N-Ab level increases in pathologic state in comparison with normal state, and their properties change. They convert to highly specific molecules binding EB with high affinity. At the initial stage of the decease, undesirable, damaging properties of EB are eliminated by this way. Thus, N-Ab level can correlate with character and severity of the disease and with therapy efficiency. An actual problem of modern diagnostics is new methods development for addiction states monitoring.
The research allowed N-Ab using for the estimation of addiction pathology development was performed. Enzyme-linked immunosorbent assay (ELISA) was used as the research tool. The levels of IgM specifically reacting with conjugated antigens of beta-endorphin, dopamine, orphanin, serotonin, histamine and angeotensine were measured in blood serum of patients. Specific change of humoral immunity was established in development of drug addiction. It appeared in increase of specific antibodies to EB levels for 60% to 80% in a group of the examined patients in comparison with healthy donors. During the treatment of drug addicts the tendency to normalization of N-Ab to opioid peptides levels was stated.
For chronic alcoholics a specific immunodeficiency was found in 87% cases: N-Ab to EB levels were decreased in comparison with donors. The levels of N-Ab to serotonin and dopamine were normalized by the end of treatment in more than a half of patients of this group.
It is established that 14 out of 20 (70%) examined pathologic gamblers had 2 times lowered levels of specific N-Ab to beta-endorphin. Normalization of these values was not observed during the treatment.
Changes in the immune system in different addiction deceases development were shown. It appears in the increase of synthesis of immunoglobulins binding bioregulators of opioid and monoamine nature for drug addiction and decrease of these values at alcoholism and gambling. The obtained data can be used for new diagnostic methods creation for addiction deceases monitoring.

ANTIBODIES TO OPIATES IN SERUM AS MARKERS OF CHRONIC DRUG USE

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The early diagnosis of drug addiction is not an easy task, and common analytical methods are not always suitable and efficient. A novel diagnostic ELISA test for the detection of antibodies following opiate use was previously developed in the Institute for Physiologically Active Compounds. The developed test allows the effective monitoring of systematic drug use 2 weeks to 4 months prior to the last drug dose.
Our investigation provides approbation of the above method in opiate abusers and correlation of the results with LC-MS analysis of opiates in hair. The ELISA test was performed in 21 opiate abusers, 15 of them were chronic users (4 to 11 years) and 6 had unknown drug usage history. The results obtained by ELISA were compared to those obtained by LC-MS in hair and FPIA in serum.
Three out of six serum samples were negative for opiates and Abs, whereas the other three were positive by FPIA, with only one positive for Abs. Since Abs are in the bound state, ELISA can not detect free Abs. Fifteen chronic users had negative FPIA results for opiates. Hair samples were analyzed by LC-MS and were divided in two groups according to the detected levels of opiates. In the first group (11 patients) with low opiate levels (LOQ-0.67 ng/mg), 7 patients (64%) demonstrated no Abs, 2 (18%) showed trace levels of Abs and 2 (18%) were positive for Abs. In the second group (4 patients), with high opiate levels in hair (from 0.78 to 1.79 ng/mg), 3 patients (75%) indicated positive results for Abs and 1 (25%) had a trace result for Abs. Medium correlations between opiate levels in hair and Abs levels (r=0.51) and between administration frequency and Abs levels (r=0.64) were observed.

APPLICATION METHODS OF ANALYTICAL TOXICOLOGY AND CLINICAL DIAGNOSTICS AT THE EXOGENOUS POISONING

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On the basis of the clinical picture, the results of laboratory research, including chemical-toxicological studies, we have shown the link disorder patients' health due to the toxic action of prohibited drugs. Integrated application of methods allows to increase the quality of diagnosis of exogenous poisoning, especially in case of chronic diseases. For example, man, 46 years old, he entered the examination to the toxicological center. In the medical history complaints against harmful working conditions. As a result of clinical examination revealed the exacerbation of chronic bronchitis and acute steatosis. When chromatomass-spectrometric study of biological fluids (urine and plasma) with the use of a gas chromatograph Crystal 5000.2 (Chromatec) with a quadrupole mass-selective detector DSQ

(Thermo) were identified metabolites terbinafine. A long-term self-treatment with antifungal drug terbinafine caused chronic intoxication with the biochemical changes. Next case, man, 36 years old, hospitalized for about drugs. In carrying out biochemical studies revealed disorder of enzymes that regulate nitrogen metabolism, the synthesis of porphyrins in the mitochondrial apparatus of hepatocytes. There are disorders of the pigment functions. Characters of toxic effects are observed in the study of blood samples under the microscope: toxic grain neutrophils, cariorexis, hypersegmentation of nucleus of neutrophils, vacuolization of cytoplasm. After chemical-toxicological study of urine was detected methadone and its main metabolite Eddp, cocaine and its metabolites. The results of the chromatomass-spectrometric research in the form of chromatograms of the total ion current and mass-spectrum of Eddp are presented in figure 1. In the study of various segments of the hair with the use of solid phase extraction and gas chromatography Maestro with a quadrupole mass-selective detector using an automatic search for a program AMDIS and with observing of three distinguished 182, 82 and 303 ions (extract ion chromatograms) identified cocaine (figure 2), methadone and its metabolite were not found.

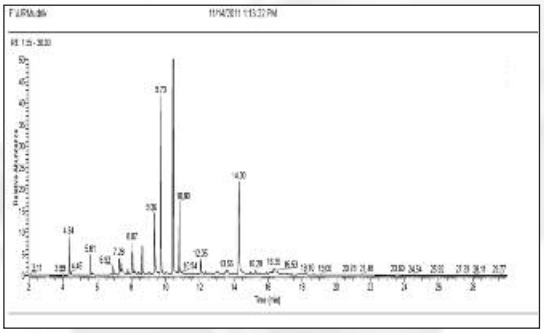

Figure 1. Total chromatogram of urine and mass spectra of Eddp.

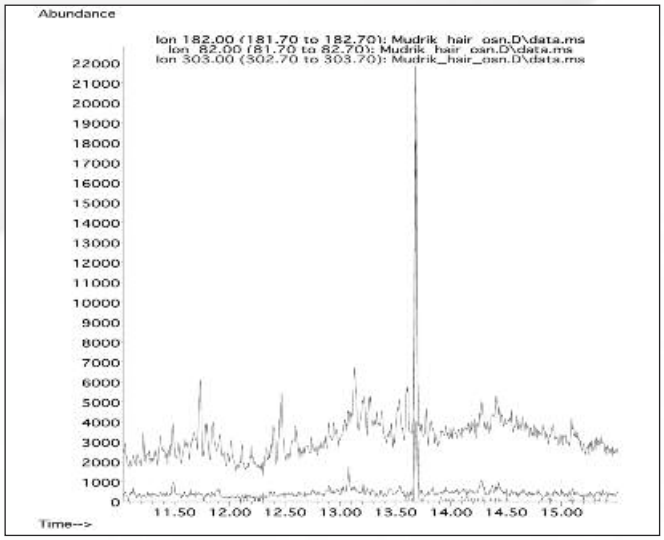

Figure 2. Extract ion chromatograms of hair with cocaine.

ORGANIZED FILMS BASED ON PHOTOSENSITIVE MEMBRANE PROTEINS AS THE KEY ELEMENTS OF NANO–BIO HYBRID STRUCTURES

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The development and study of hybrid nano-biomaterials engineered from photosensitive membrane proteins (the key functional elements of various biomembranes) and nanoheterostructures (inorganic nanoparticles, transparent electrodes and films, colloidal quantum dots, etc.) is a rapidly growing field at the interface of materials and life sciences, with potential implications for nanotechnology and biomedicine. The main achievements in this field are related to self-assembled films prepared from purple membranes (PMs), bacteriorhodopsin (bR), reaction centers (RCs) of some bacteria and plants, etc. These ultrathin, highly oriented PMs-, bR-, or RC-based films may be tagged with fluorescent semiconductor quantum dots or plasmonic nanoparticles capable for harvesting additional solar energy and transferring this energy to the photochromic biocomponent of the fabricated films. The resultant systems may be regarded as bio–nano hybrid materials exhibiting enhanced biological function or nanodevices characterized by advanced photovoltaic, energy transfer, or optical switching properties.
Comparison of the techniques for obtaining thin films and their structural and functional characteristics leads to the conclusion that the homogeneity and orderliness of PMs, bR or RCs in these films depend on the method of their fabrication and increase in the following order: electrophoretic sedimentation < Langmuir–Blodgett (Langmuir–Schaefer) method < self-assembly and layer-by-layer methods. The techniques of preparation of nano–bio hybrid structures composed of photosensitive membrane proteins and semiconductor fluorescent quantum dots or plasmonic nanoparticles and demonstrated advanced photovoltaic properties are also analyzed.

LIPID-PROTEIN NANODISCS: ALTERNATIVE TOOL FOR PRODUCTION, STABILIZATION, STRUCTURE-FUNCTIONAL STUDIES AND DELIVERY OF MEMBRANE BIOMOLECULES

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Membrane proteins (MPs) play key roles in many biological processes essential for living cells, whole organisms and their communities. These molecules are responsible for cell energetics, reception of intercellular signals, as well as for functioning of nervous, endocrine and immune systems of higher animals. About one quarter of the human genes are predicted to encode for MPs and more than 50% of current pharmaceutical drugs target membrane proteins. MPs provoke much interest due to their perspective application in biotechnology (membrane enzymes), bio-nanotechnology (chemical sensors, photoactive proteins), pharmacology and medicine (membrane receptors, membrane-active drugs, delivery of hydrophobic compounds). The practical applications and fundamental studies of MPs are significantly complicated. For example, from about 30,000 presently known protein structures only about 200 ones (< 1%) represent integral MPs. The main difficulties in this field are connected with the requirement of biological membrane or suitable membrane mimicking medium for formation and stabilization of MPs native spatial structure.
The commonly used membrane mimetics (low-polarity organic solvents, detergent micelles and bicelles) display some serious shortcomings and in many cases do not able to adequately represent membrane environment and provide enough stability for encapsulated MPs. On the other hand, the real bilayered systems (in a form of lipid vesicles) are too large to be used directly in biotechnological and pharmacological applications and in fundamental studies. The present report describes the possible applications of an alternative membrane mimicking medium – Lipid-Protein Nanodiscs (LPNs). Each LPN represents a fragment of lipid bilayer stabilized by a dimer of human apolipoprotein A1 or it synthetic analogue. These particles have discoid shape with diameters 8 - 12 nm and thickness about 4 nm. The integral and peripheral MPs, membrane active peptides and other hydrophobic compounds could be incorporated into bilayer of nanodisc using "self-assembly" protocol. The LPNs provide superior membrane mimicking characteristics and enhanced sample stability as compared with conventional membrane mimetics. In contrast to micelles and liposomes nanodiscs permit to control the aggregation state of the encapsulated MPs. The application of nanodiscs for cell-free production and refolding of recombinant MPs, for biochemical and structural studies of membrane receptors as well as the possible usage of nanodiscs for delivery of hydrophobic compounds are discussed in the report.

COMPUTER ASSISTED SELECTION OF OPTIMAL MONOMER FOR IMPRINTING OF TRI-O-ACETYLADENOSINE IN POLYMER MATRIX

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Molecularly imprinted polymers can be anticipated as synthetic imitation of natural antibodies, receptors and enzymes. In case of successful imprinting the selectivity and affinity of the imprint for the imprinted substrates are comparable with those of natural counterparts. The selection of the optimal functional monomer, monomer/template ratio as well as selection of polymerization solvent is crucial determinants of the successful imprinting. In the present study this is assisted by the computer calculations of the pre-polymerization complex energy by quantum mechanics/molecular mechanics (QM/MM) ab initio approach. The energy of the prepolymerization complexes of tri-O-acetyladenisine (TOAA-template) with three different monomers – methacrylic (MAA) acid, 3-vinyl benzoic acid (VBA) and acrylamide (AA) were calculated. On the basis of these calculations it is shown that the strength of the pre-polymerization complex substantially decrease in the series MAA>VBA>AA. The same conclusions are made from self-consistent field calculations of pre-polymerization complex energy. In both approaches the calculations were based on the hydrogen bonds formation between template and monomer.
By imprinting TOAA into polymer matrix the synthetic reproduction of Adenosine triphosphate (ATP) binding site to protein kinases can be fabricated and further used for ATP- analogs screening in different sources. Computer calculation can substantially accelerate and guide the development of optimal protocol for efficient template imprinting.

MICROBIAL SYNTHESIS AND PROPERTIES OF 3-HYDROXYBUTYRATE AND 4-HYDROXYBUTYRATE COPOLYMERS

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Global dependence of humanity on petroleum-derived plastics increases greatly every year. However, as the oil store is exhausted and people acquire a better understanding of the harmful effects of petroleum-derived plastic materials in the environment, they try to find an alternative to them. Polyhydroxyalkanoates (PHA)s could be an appropriate replacement for petroleum-derived plastics. PHAs is a class of microbially stored polyesters consisting of chiral R-hydroxyalkanoic acids. Physical and chemical properties of PHAs are similar to those of polyolefins, but in contrast to plastics they are biodegrad-

able and biocompatible; therefore PHAs can be used in agriculture, medicine, pharmacology, industry. Properties of PHAs are determined by the PHA structure. Copolymers of 3-hydroxybutyrate (3HB) and 4-hydroxybutyrate (4HB) have been found to exhibit particularly useful material properties relative to other PHAs. However, synthesis of PHAs of a definite structure is a technological challenge; therefore, PHAs of a definite structure can only be produced based on the fundamental knowledge of their synthesis. Thus, this study addressed synthesis of copolymers of 3-hydroxybutyrate and 4-hydroxybutyrate by the bacterium *Cupriavidus necator* B5786 and properties of the copolymers. Bacterial cells were cultured under special conditions of carbonic nutrition (with such sources of carbon as fructose, butyric acid, γ-butyrolactone and 1,4-butanediol as sources of 4-hydroxybutyrate). To find favourable conditions for maximal accumulation of copolymers with high content of 4-hydroxybutyrate, different culture conditions were studied. The duration of fed-batch cultivation, quantity and concentration of the feed, adding of co-substrates (propionic acid, acetic acid) were studied. A set of highly purified samples of P(3HB-*co*-4HB) with different content of 4HB (from 8.7 to 24.3 mol.%) was produced. It has been determined that the incorporation of 4HB in the copolymer leads to the decrease of the copolymer's crystallinity; samples with the crystallinity of 12% and 25% have been obtained. It has been demonstrated that the average molecular weight of the P(3HB-*co*-4HB) samples and the polydispersity do not depend on the ratio of monomers and vary within the wide range from 540 to 1100 kDa and from 1.91 to 2.76 correspondingly.
The study was financially supported by the project "Biotechnologies of novel biomaterials" (Agreement No. 11.G34.31.0013) in accordance with Resolution No. 220 of the Government of the Russian Federation of April 9, 2010, "On measures designed to attract leading scientists to the Russian institutions of higher learning" and the Program of the President of Russia for young Doctors of Sciences (Grant No. MD-3112.2012.4).

MULTICELLULAR TUMOR SPHEROIDS FORMATION IN POLYELECTROLYTE MICROCAPSULES USING RGD-PEPTIDES

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Three-dimensional model of solid tumor, namely multicellular tumor spheroid (MTS), is now routinely used in many scientific laboratories to screen anticancer drug safety and efficacy. MTS formation in polyelectrolyte microcapsules as an effective strategy to generate uniform MTS has been proposed by us recently [Zaytseva-Zotova et al. (2011) J Biomed Mater Res B Appl Biomater. 97(2):255-62]. In comparison with classical methods, microencapsulation is a versatile technique that allows to form MTS from various cell types with different growth properties. However, for several tumor cell lines it is impossible to generate MTS even using microencapsulation. In this work, we propose to encapsulate cell aggregates instead of single cells, in order to promote cell growth and subsequent MTS formation in microcapsules.
Murine melanoma (M3) was chosen as a model cell line. Cell aggregation was induced by incubating cells in culture media containing novel RGD-peptides (0,1-100 uM) and 10% FBS. Cell morphology and viability were monitored visually using optical microscopy and by MTT assay.
It was found that cells began to form aggregates within the range of 48 and 72 hours of cultivation in the presence of RGD-peptides. We've observed a reduction of M3 growth rate when the aggregation process was lunched. However, cells in aggregates remained viable. It should be noted that using a novel RGD-peptides we succeeded to induce M3 aggregation even at low peptide concentrations (1 uM). The resulted aggregates of M3 cells had a mean diameter of 110 um and were shown to be uniform. On the next step the obtained aggregates were encapsulated in alginate-oligochitosan microcapsules. Cell aggregates increased in their sizes and filled the whole microcapsule volume in 14 day after encapsulation. In contrast, being encapsulated as single cells, M3 cells grew on the inner microcapsule membrane but did not fill microcapsule volume.
Thus, our results indicated that encapsulation of M3 aggregates allowed to promote M3 cell growth and subsequent MTS formation within microcapsules. Furthermore, cell treatment with RGD-peptides could be proposed as a novel simple method for generation of unimodal aggregates.

HYDROGEN-BASED BIOSYNTHESIS: BIOTECHNOLOGY OF CHEMOLITHAUTOTROPHIC HYDROGEN-REDUCING ORGANISMS

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Researchers of the Institute of Biophysics of the Siberian Branch of the Russian Academy of Sciences are engaged in comprehensive investigations of PHAs, including biotechnological studies aimed at synthesizing polymers differing in their chemical composition, studies of PHA structure and physicochemical properties, engineering development of the technology, testing of the techniques to fabricate special polymeric items, and biomedical studies. We have already developed processes of synthesizing variously structured PHAs, using different substrates, studied physicochemical properties of

the polymers and shown controllability of some of these properties (degree of crystallinity, thermal properties, and biodegradation rate). The first Russian Pilot Production Facility for fabricating PHAs has been put into operation – project ISTC. The obtained results are legally protected and the prepared polymer has been registered and trademarked as Bioplastotan™; These findings made it possible, for the first time in practical biotechnology, to synthesize high yields of polyhydroxyalkanoates from products derived from brown coals via modified gasification procedure.
We investigated highly purified PHA samples produced at the Institute of Biophysics SB RAS and synthesized by bacteria *Ralstonia eutropha B5786* using the technology that allows to obtain PHAs having various chemical structures and high degree of purity, applicable for medical purposes, including contact with blood. Using PHAs in various phase states (solutions, emulsions, powders) we produced and investigated the structure and properties of two- and three-dimensional matrices in the form of flexible transparent films, membranes, superfine fibers, microparticles, sponges, three-dimensional solid and porous constructions. We demonstrated the possibility of application of conventional methods for sterilization of matrices without changing of the structure, loss of strength and deterioration of surface adhesion properties. With the help of microscopy, detection of protein synthesis and DNA by the cultivated cells, MMT test, it was shown that in the cultures of fibroblasts, hepatocytes, endothelium cells and osteoblasts PHA-matrices haven't cytotoxicity at direct contact with any of the investigated cells and that the cells can be cultivated *in vitro*.
The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and the Program of the President of Russia for young Doctors of Sciences (Grant No MD-3112.2012.4).

MACROPOROUS HYDROGEL OF POLYVINYL ALCOHOL FOR MEDICINE

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The present-day development of medicine and other sciences and technologies connected with human health requires creation of new highly-effective and harmless materials which allow to broaden possibilities of surgical, therapeutic and bio-analytical methods and systems.
In this study novel method of creation of macromolecular materials for medical application on the basis polyvinyl alcohol macroporous hydrogels is proposed. Polyvinyl alcohol finds wide application for medicine, hydrogels on the basis of polyvinyl alcohol also attracts great attention. However, easily prepared physical gels of polyvinyl alcohol formed by freezing of its aqueous solutions are unstable and readily turn reversibly into solution.
Suggested novel method of preparation of polyvinyl alcohol hydrogels consists in formation of polymeric network by cross-linking of unsaturated derivatives of this polymer. Such method allows to form macroporous systems with broad set of pores of dozens and hundreds micrometers size, and stands out due to their high stability and good swelling capacity in water and salt solutions. It is also very important that obtained cross-linked products were made on the basis of beforehand synthesized and characterized polymers and that is why did not contain residua of monomers and other toxic agents.
Investigation of the influence of reaction conditions on the formation of porous gels allowed revealing of the conditions which provides reproducible preparation of the final product with high yield and adjusted overall porosity, pores size, polymer cross-linking degree. Investigation of interaction of synthesized hydrogels with living organism tissues showed that introduction of developed preparation do not provoke inflammatory reaction on the initial stages of traumatic process and during the long-term contact novel hydrogels biodegrades fully with their substitution by conjunctive tissue.
High biocompatibility, biodegradation with adjusted speed, good mechanical properties, stability under the conditions of application of standard sterilization methods, ability to sorb considerable amounts of liquids including salt solutions without changing of volume characteristics, availability of parent substances and of preparation methods allowed to propose obtained materials for medical application, especially in thoracic surgery, for treating of trophic ulcers and burns, in cosmetic surgery, for creation of therapeutic systems with controlled release of active substance and in several other areas.

POLYURETHANE BIOMATERIALS AS ANTITUBERCULAR DRUGS CARRIERS

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Polyurethanes are widely used as biomaterials for several medical devices because of their excellent mechanical properties and relatively good biocompatibility. The goal of the present work is development of polymeric biomaterials such as polyurethane foams and polyurethane microparticles as carriers for controlled release of antitubercular drugs for treatment of tuberculosis. Polyurethane foams with different content of hard and soft segments were synthesised by a two-step polymerization using a number of polyethylene and propylene glycols and tolylene-2,4-diisocyanate. Antitubercular drugs isoniazid or rifampicin were incorporated into the polymeric matrix at first

stage. The release behaviour of antitubercular drugs from polyurethane foams was examined by means of immersing the polymeric samples in a modelling biological medium at 37°C and subcutaneous implantation at animal organism. All the release data show the typical pattern for a matrix controlled mechanism. The total amount of drugs was released in 5-30 days in dependence of loading of drugs and contents of high segments in polymer.
The second type of polyurethane biomaterials is the polymeric microcapsules containing antituberculous drug for targeted delivery of drug by respiratory way. Administration of microparticles to the lungs (alveolar region) may provide the opportunity for the prolonged delivery active agent to tuberculosis infected macrophages. Polyurethane microcapsules incorporated with antitubercular drugs were synthesized by interfacial polyaddition reaction between toluene-2,4-diisocyanate and various polyethylene glycols (PEG) in water-toluene emulsion. It was shown that the size of polymeric microcapsules and size distribution are important factors for their application for pulmonary administration of drug by respiratory way. The influence of different conditions of synthesis such as water/PEG ratio, molecular weight of PEG and drug concentration on the release behaviour of drugs from microparticles was investigated. The increase PEG content in water phase of reaction, results in decreasing drug diffusion, due to formation of polyurethane microparticles with denser polymer wall. Increasing molecular weight of soft segments (PEG) results in the increase of diffusion rate of drug into solution. This phenomenon can be attributed to increasing molecular weight of PEG which leads to accelerating diffusion of water-soluble drug through hydrophilic PEG chains. Polyurethane miroparticles with higher drug loading demonstrate faster release rate of the drug due to increase gradient of concentrations between the external solution and core of microparticles. The antitubercular effect of polyurethanes was tested using disc diffusion method against a museum strain of *Mycobacterium tuberculosis*. Minimal suppressing concentration for polymeric systems was 0,025 – 0,05 mcg/ml. The tuberculostatic activity of drugs released from the polyurethane show antimicrobial activity identical of low molecular drugs. The efficiency of the tuberculosis treatment by polyurethane drug delivery systems was shown in experiments on animals. The treatment of animals infected with tuberculosis be polyurethane systems was more effective than the treatment by free drugs. Isoniazid released from polyurethane systems was 1.5-2 times less toxic in comparison with the low molecular drug. Minimal toxic action of polyurethane on the native organism tissue was established hystologically. Medical-biological tests show that polyurethane ensures sustained release of antitubercular drugs and maintains effective drug concentration for long time. The results obtained in the present work have shown the possibility and outlook of polyurethane as carriers of antitubercular drugs for the delivery systems for prolonging the action of chemotherapeutical agents in tuberculosis treatment.

A COMPARATIVE STUDY OF CELL CULTURE MATRIXES PREPARED FROM RESORBABLE POLYHYDROXYALKANOATES OF DIFFERENT CHEMICAL COMPOSITIONS

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Requirements to materials for tissue engineering are strength, simple processing, biodegradability, biocompatibility, ability to stimulate cell differentiation and proliferation. Polyhydroxyalkanoates (PHAs) are thermoplastic biodegradable and biocompatible polyesters of bacterial origin. PHAs have useful properties therefore they could be used in cell and tissue engineering for regeneration of damaged skin, wound closing of soft and bone tissues, production of blood vessel implants and cardiac valve bioprosthesis etc. Physical and mechanical properties of PHAs depend on monomer compositions of PHAs that could be from high crystalline thermoplastics to elastic copolymers.
Aim of this work was construction and comparative study of properties of cell matrixes made from PHAs of different chemical composition.
Materials and methods. We used PHAs, synthesized in Institute of Biophysics SB RAS: homopolymer of 3-hydroxybutyric acid and copolymers 3-hydroxybutyrate and 3-hydroxyvalerate, 3-hydroxyhexanoate and 4-hydroxybutyrate. Composition and structure of polymers were studied using gas chromatography, X-ray structure analysis, gel permeation chromatography. Thermal properties were studied by differential-scanning calorimetry. Matrixes were made by casting a polymer solutions. Matrixe microstructure was studied by scanning electron microscopy, atomic-force microscopy, surface properties were studied on basic of measuring of contact wetting angles. Cell adhesion and proliferation were assessed using mouse fibroblast NIH 3T3 line. Cell cultivation was carried on 7 days. Cells on matrixes were stained with eosin or DAPI to count cells and assess cell morphology. Cell proliferation was studied by MTT assay.
Results. Matrixes from PHAs of different chemical compositions have been constructed. Copolymers with 3-hydroxyvalerate have most smooth surface, copolymer with 3-hydroxyhexanoate has most relief surface. Reduction of contact wetting angles of copolymers as compared with poly-3-hydroxybutyrate shows that copolymers are more hydrophilic and suitable for cell supporting matrixes. Surface of all studied types of PHAs sustains cell adhesion and proliferation. Fibroblasts on all matrixes have typical morphology over all experiment.
Results of experiment shows that all studied types of PHAs may be used for construction of cell supporting matrixes.
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P 01

NANOEMULSION FOR CONTINUOUS PARENTERAL INFUSION OF TAXANES

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Today class of taxanes is one of the best antineoplastic drugs found from nature. Taxanes have been found to be effective against many forms of cancer according to the data of the National Cancer Institute (NCI, USA) in the past decades. Taxanes, as well as most anticancer drugs, have limitations in clinical administration due to their poor water solubility. It considerably prevents injection of appropriate high drug dose. For example, derivative of taxanes paclitaxel demonstrates extremely poor water solubility (0,05% mass) while requested dose is upward through several decades. New perspectives appeared along with using nanoemultions oil in water (o/w type) for taxane water solubility improvement. Such systems can be made from either natural lipids or synthetic surfactants. They form the internal phase like a hydrophobic compartment for the drug inclusion and the hydrophilic outer phase. The lipid containing nanoemulsion seems to be a promising medicinal form that could solve the problem of poor water solubility and reduce systemic toxicity providing release prolongation.
Standard chemotherapeutic technique includes continuous parental infusion of drugs. A treatment with 3- or 24-hours intravenous infusion is accepted depending on regime (dose, combination therapy).
The purposes of the investigations were to study the opportunities of the taxane containing nanoemulsion parenteral infusion, multifold dilution, increase of stability in aqueous infusion solution during procedure time.
The paclitaxel and docetaxel containing nanoemulsions of oil-in-water type (o/w) with nano-scale particle sizes (<500 nm) were obtained. The concentration of the drugs was more than 10 mg/ml. The taxanes loaded lipid containing nanoemulsion appeared to be one of the most convenient systems for continuous parenteral infusion due to high drug solubilization capacity taxanes as well as considerable increase of water solubility and prolongation of the drug release process. The opportunity of the 24 h continuous infusion in aqueous infusion solution, the circulation of the drug concentration in the blood was shown. According to the required techniques the drug formulation was diluted in a ratio of 1:10 and 1:20 with saline dextrose infusion solution. The system was found to be stable for a day or two. Dialysis modeling drug circulation in blood plasma demonstrated increase of taxane containing nanoemulsion stability for a long time and prevention of active compound fast release.
Investigations were financially supported by Russian Ministry of Science and Education (grant No11.G34.31.0004).

P 02

APPLICATION OF AC MAGNETIC FIELD INCREASES ACTIVITY OF SUPEROXIDE DISMUTASE 1 IMMOBILIZED ON THE SURFACE OF IRON OXIDE MAGNETIC NANOPARTICLES

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Nanomedicine formulations aim to improve the biodistribution and the target site accumulation of systemically applied therapeutics. Theranostic nanomedicine formulations offer both the visualization of drug distribution and drug release at the target site, while the optimized strategy is both triggered drug release and the prediction and monitoring of therapeutic responses. Example of such systems is metal nanoparticles, which can be used for both MRI imagining and drug loading.
The goal of this study is preparation of iron-oxide magnetic nanoparticles, immobilization of superoxide dismutase 1 (SOD1) on particles surface and evaluation of changes in enzymatic activity following exposure to AC magnetic field.
Methods.
First, iron oxide magnetic nanoparticles (MNPs) were coated with $mPEG_{5K}$-b-$PLKC_{100}$ block-copolymer. Second SOD1 was immobilized on polymer-coated MNPs. MNPs solution (in DI water) was added dropwise to SOD1 solution (in HEPES, pH 7.4). The unbound enzyme was removed by centrifugal filtration, the MNPs concentrate was washed with HEPES buffer and reconstituted with 10 mM HEPES buffer, pH 7.4 or 10 mM HEPES-buffered saline, pH=7.4. The solution was filtered through a 0.2 mm Teflon filter. The protein concentration in MNPs was determined by ICP-MS (by the ratio

of Cu to enzyme). The size and surface charge of the nanoparticles was determined using DLS. Immobilized enzyme activity before and after magnetic field application was measured using pyrogallol autoxidation.

Results and discussion.

Salt addition into HEPES buffer confirmed the electrostastic nature of binding between negatively charged SOD1 (at pH=7.4) and positively charged polymer-coated MNPs.

Size of new formulations was 86,1±0,2 nm and s-potential (–12,2±0,3) mV. Concentration of SOD1 on the surface of MNPs was 3,36 μg/mL.

Immobilization of SOD1 resulted in decrease in activity. But it's interesting to note that after field application activity of enzyme increased. It might be associated with release of enzyme.

In **future studies** we would like to optimize the filed strength and/or exposure time to further increase the enzymatic activity. We will also evaluate the stability of MNPs-SOD1 complex in vivo.

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P 03

POROUS BIOACTIVE GLASS-CERAMIC MATERIALS FOR BONE PROSTHESIS

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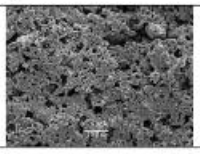
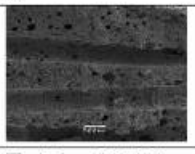
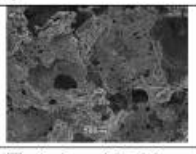
Nowadays neorganic calcium-phosphates are prosperously used as implant materials for bone trauma and injury curing because of their bioactivity i.e. the ability to accrete with bone tissue without incapsulation and rejection processes. Such materials must possess high pore structure including open pores with diameter 100-1000 μm to allow blood vessels and bone cells growing inside material and pores with diameter 10-100 μm to permeate physiological solutions after implantation. Glass-ceramic technology opens up opportunity for the design of biomaterials with directed and adjusted physiological action for the specific application according to medical indications because of the possibility of a wide structural parametres variation and thereby biochemical processes kinetics control inside the human body after implantation.

The purpose of the study was to achieve listed over properties in glass-ceramic materials, based on bioactive calcium-phosphate glass with CaO/P_2O_5 ratio 1,1. Materials were obtained by means of ceramic processing using combustible pore-formers – granules and bars of paraffin, starch, NH_4OH, NH_4NO_3, graphite and nylon with diameter from 50 to 2000 μm. Glass powders dispersion in slurries was varied from 40 to 400 μm. Sintering was conducted at temperature 900 °C during 1 hour.

Following methods of forming raws for sintering were used: glass powders molding with starch acting as gas-forming agent, glass powders molding with bars acting as channel pore-forming agents, mixing slurries with granules acting as cell pore-forming agents. Immiscible fluids technique (oil + gelatin slurry) was used to form porous glass-ceramic granules. Using these four forming methods allowed to obtain correspondingly four series of materials with different pore structures (see table):

No	1	2	3	4
SEM Photo, x50				
Open porosity, %	25-50	Total – 25-50 Channel– 5-15	Total – 40-80 Cells – 20-60	10-30
Pores sizes, μm	10-200	Interchannel – 10-200 Channel – 480-530	Intercellular – 10-40 Cells – 100-2000	Intergranular – 5-20 Granules sizes – 200-1000
Compressive strength, MPa	5-30	3-30	1-30	-

Materials implantation in rabbits for a period from 2 to 12 months showed absence of encapsulation with connective

tissue. Intensive biointegration of bone cells inside pore structure occured in 4 months on average. All pore space is filled with bone tissue and blood vessels in 12 months. Higher porosity level leads to higher rate of material coalescence with bone. Thus, neogenic bone tissue forms in 2 months of implantation inside materials with 55 % open porosity, and only in 4 months of implantation inside materials with 30 % porosity.

P 04

CATALASE AND SUPEROXIDE DISMUTASE NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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Numerous central nervous system (CNS) disordes accompanied with activation of microglial cells, which is linked to overproduction of the reactive oxygen species and subsequent neuronal damage. The use of the antioxidant enzymes (such as superoxide dismutase, SOD, and catalase) is considered for therapy of pathological processes in CNS. For the treatment antioxidant enzymes should be resistant to proteolysis and able to overcome the blood-brain barrier. A possible solution is to modify the catalase and SOD to the subsequent intravenous injection of. The aim of this work was to obtain the immobilizing active enzymes in cross-linked nanoparticles.
Formulations of antioxidant enzymes were prepared by electrostatic coupling of these enzymes with cationic block copolymer (poly(L-lysine)-poly(ethylene glycol), followed by covalent cross-linking with glutaraldehyde to stabilize nanoparticles.
Obtained catalase and SOD nanoparticles were 40 nm and 20 nm in size respectively. The loss of catalase activity not exceeded 50%, the loss of SOD activity is about 70%.
According to gel-chromatography of catalase nanoparticles on Sephadex G-200 aggregates of 40 nm retained 50% of the initial activity, and aggregates of larger size lost activity. Preservation of catalase activity in 10^{-6}M solution of trypsin was investigated. Whereas initial catalase lost about 80% of enzyme activity, modified catalase lost about 50 % of enzyme activity after 3 h of incubation in the presence of trypsin.
Thus, active and stable to proteolysis catalase and SOD nanoparticles were obtained, giving perspectives to overcome the blood-brain barrier and deliver the enzyme in the CNS.

P 05

DEVELOPMENT BY LEACHING TECHNIQUE THE NANO-SIZED OPEN POROSITY IN ULTRA HIGH MOLECULAR WEIGHT IMPLANTS

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Commercial solid (nonporous) implants based on Ultra High Molecular Weight Polyethylene (UHMW PE) exhibit serious disadvantage for human life such as generation of fine polymer particles which cause some negative even lethal effects. These fine solid particles generate as the result of high friction between the artificial implant's parts because of absence of internal natural lubricant (synovial liquid) inside the implant body as the natural implants have. Just external lubrication of implant's surface is not enough to prevent mechanical erosion of implants. Extremely high viscosity of UHVW PE melt makes impossible to produce the porous structure by the regular foaming techniques. To make an open pore structure of implants which should be fully permeable for synovial liquid and delivery it from inside to outside surface of implant, it has been developed a novel family of implants based on leaching technique. The UHMW PE melts have been mixed with nano- and micro-sized solid salts, put in the mold, put in the water bath and chilled down to the solid state. After words the particles of solid salts have been dissolved and leached by water. The leaching time is controllable decreased at the elevated temperature of water or other dissolving liquids. Several commercial mineral salts have been tested and the optimal particle size distribution has been studied. The developed open pore implants have controllable nano- and micro-sized interconnected pores and they promote to migrate the natural lubricate synovial liquid to the external surface of implants to decrease the friction between the parts of implants and thus prevent generation of fine solid polymer particles dangerous for human health.

P 06

ARTRIFICIAL POROUS WOOD WITH NANO-SIZED STRUCTURES BASED ON MINERAL WASTE

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It has been developed formulations and continuous extrusion process for industrial manufacturing of eco-friendly and inexpensive thermoplastic-based Artificial Porous Wood which helps to resolve some urgent global problems such as: deforestation and saving of billion tons of natural wood, reduction of carbon dioxide and other Greenhouse Gas (GHG) emission in atmosphere, increasing of oxygen in atmosphere, prevention of the global warming, and conversion to useful products many billion tons of both plastics and mineral waste.
The novel generation of Artificial Porous Wood (APW), which belongs to organic-mineral gas-filled reinforced composites, has porous structure similar to the natural wood with high density solid skin and low density foamed core zone. Porosity, created by foaming process of the polymer binder, provides several very useful properties of APW, such as light weight, excellent thermal- and cold-insulating ability, buoyancy, energy conservation, sound attenuation. For porous binders have been used both thermoplastic virgin or waste plastics. For fillers have been applied very inexpensive mineral fillers such as by-products of power plants as well as other mineral waste. The APW has nothing to do with the commercial types of WPC – Wood Plastic Composites, because does not contain any natural wood waste such as wood flour, sawdust, cellulose fibers, etc.
In addition to the micro-sized gaseous cells (pores) and solid fillers the developed APW contains nano-sized solid mineral fillers. The content of nano-structures depends on selection of solid filler with proper particle-size distribution. It has been demonstrated that for optimal mechanical properties the content of solid nano-fillers should not exceed 10% of all solid particles. The presence of nano-sized structures improves significantly both extrusion processability and mechanical properties of Artificial Porous Wood.

P 07

DOUBLE NANO-SIZED GAS AND SOLID STRUCTURES IN FOAMED COMPOSITES

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It have been developed fire-resistant foamed composites are based on thermosetting resins as binder and mineral waste as fillers. The composites exhibit the unique combination of the following properties: Not-Combustive and Non-Smoldering, Don't Generate Hazardous Substances during Manufacturing and Application, Very High Thermal Resistant (Very Low Thermal Conductivity), Very Broad Range of Density and Strength, Very High Chemical and Biological Resistance, Environmentally Friendly Raw Materials, Less Expensive that Polystyrene and Polyurethane Foams. The main application of the developed materials is external and internal fire-resistant thermal insulation in construction industry for hospitals, civil and industrial buildings.
The developed composites produced by casting, free-rising, cold-curing technology without application of external heat and pressure. The resin with powdered mineral fillers mixes for 30 sec with blowing-curing agent and decants to any cavity where the mixture starts to foam and the foaming process is over within 2-3 min. The density of the foam varies form 30 to 500 kg/m^3 depends on the content of blowing agents and solid filler.
In addition to micro- and macro-sized structures the developed materials contain two types of nano-sized structures: gaseous cells (pores) and solid fillers. The volume of gaseous nano-cells does not exceed 10% of all cells, but their amount about 1000 times more than other cells. The size and amount of nano-cells controls by foaming kinetics and expansion ration of the mixture. The content of nano-sized solid filler controls by selection of particle size distribution of filler and does not exceed 10% of all other solid particles. It was demonstrated that the ratio between nano-gas cells and nano-solid fillers is able dramatically changed the mechanical and thermal insulation properties as well as fire resistant characteristics of the composites but does not change the overall density. The positive effect of co-existence of such double nano-sized structures belong to different aggregate states (gaseous and solid) might be useful both for academic study and practical application.

P 08

CO-POLYMER PEG-CHITOSAN AS A PERSPECTIVE STABILIZING ADDITIVE FOR ANIONIC LIPOSOMES

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Liposomes are of great interest in biotechnology, as a drug delivery systems, due to their biocompatibility and low immunogenicity. However, low stability and tendency to aggregate still limits their application in medicine. Therefore, the actual problem is to obtain the effective stabilizing additives for the liposomes on the base of polymeric materials. Chitosan is a promising polymer in terms of using it as a stabilizing additive due to its biodegradability. However, chitosan is poorly soluble in alkaline solution, which interferes with the complex formation.
In this paper, the synthesis of co-polymer of chitosan (MW 90-120kDa) modified with PEG molecules (mPEG-suc-NHS, MW 2kDa) was carried out. The degrees of modification were 15% and 25%. The co-polymer PEG-chitosan was completely soluble in a wide range of pH values and still contained the free amino groups capable to interact with anionic groups of liposomes. IR spectroscopy was applied to investigate the influence of the complex formation of PEG-chitosan on the structure and stability of mixed anionic liposomes of dipalmitoylphosphatidylcholine (DPPC) and cardiolipin.
It has been found from the analysis of the IR spectra that the co-polymer PEG-chitosan forms a complex of electrostatic nature by interaction with the anionic groups in liposomes. It was determined that the binding sites of the copolymer with liposomes are phosphate and carbonyl groups. Interaction with the copolymer lowers the fluidity of the bilayer, stabilizing the gel. Analysis of the melting curves showed an increased phase transition temperature by 8 degrees in the complex compared to free liposomes.
Analysis of the IR spectra yields that the complex formation of liposomes with PEG-chitosan resulted to stabilization of liposomes against aggregation. In contrast, the complex of liposomes with free chitosan showed aggregation upon storage. This result is particularly important, taking into account the fact that the aggregation is one of the key factors limiting the use of liposomes in medicine.
These results offer the prospect of the co-polymer PEG-chitosan as an effective additive for stabilizing liposomes and holds promise for creating new drug delivery systems.

P09

CALCIUM-PHOSPHATE GLASS-CERAMIC BIOMATERIALS – STRUCTURE AND SOLUBILITY

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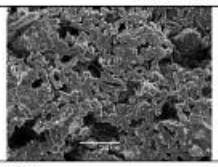
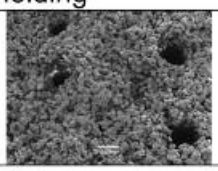
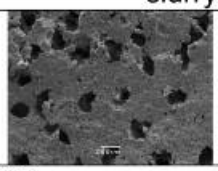
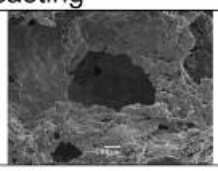
Bioactive glass-ceramic materials based on glasses of silicate and phosphate systems are capable to contact with adjoined bone tissues without incapsulation with connective tissue. The primary disadvantage if these materials is low resorption rate, that depends on chemical composilion of material and material-to-environment contact area. Investigations of materials series that possess identical chemical and phase compound (see table) in distilled water and simulated body fluid (SBF) at the temperature 37 °C and thermostating periods of from 1 to 350 hours allows to predict their behaviour inside living organism and reveal degradation processes control parameters. Examined parameters estimated to be responsible for materials degradation were: mass loss, calcium ions concentration and pH of testing solutions.

Phase composition	$Ca_2P_2O_7$, TiP_2O_7, ZrP_2O_7			
SEM Photo, x100	semidry molding		slurry casting	
				
Open porosity, %	30	45	60	75
Pores sizes, μm	60-150	500/100-160	80-120/5-40	500-2000/5-40

During materials thermostating in water concentration of calcium ions and mass loss of matrials increase and pH of water decreases. Direct relation between open porosity value, pores sizes and mentioned parameters was revealed. Thus, minimal mass loss and calcium ions concentrations are observed for materials with uniform pore structure and porosity 40-45 %, and maximal ones – for materials with cellular pore structure and porosity 70-75 %. For matrials with channel pores (the 1-st material – porosity 50 %, diameters of channels 480-520 mm, the 2-nd material – porosity 60-65 %, diameters of channels 100-120 mm) values of mass loss and water pH are comparable.
During materials thermostating in SBF the same regularities of porosity influence on materials solubility are revealed. Few differences in behaviour comprise low mass loss that is close to zero percent, though calcium ions concentration is a little higher than in water at the same thermostating periods. SBF pH is reduced insignificantly to 6,3-6,4, whereas water pH is reduced to 4,8-5,1. Such changes of main SBF characteristics and appearance of precipitation on the materials surface after first three days of thermostating indicate the following processes flowing:
- glass-ceramic material surface dissolution;
- poorly soluble calcium-phosphate compounds formation in solution;
- poorly soluble compounds precipitation on the surface of material.

The obtained results for materials with different pore structures behaviour in different water environments indicate that in macroporous systems with open porosity 40-75 % and pores sizes more than 100 mm mass loss is directly depends on open porosity value and slightly depends on pore structure configuration. In systems with pores sizes less than 100 mm direct relationship "open porosity – mass loss" is not revealed. In this case more significant parameters are pore structure and pores configuration, that provide reaction environment penetration into different parts of material surface.

P 10

POLYHYDROXYALKANOATE MICROPARTICLES AS A PLATFORM FOR DRUG DELIVERY

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Designing of controlled drug delivery systems (DDS) is a promising and rapidly developing line of biotechnology and experimental pharmacology. About 25% of the drugs sold in the world at the present time are administered via transport/delivery systems. The principal requirement for fabricating prolonged-action controlled-release drug delivery systems is availability of an appropriate material, which must be absolutely harmless to an organism and possess the necessary physical-mechanical and biomedical properties, including degradability in biological media. Polyhydroxyalkanoates (PHAs) are good candidates for fabrication of drug delivery systems, because they possess all the properties required of materials for these systems. These polymers are biocompatible and inert towards animal tissues.
The purpose of this study was to design and examine PHA polymer matrices in the form of microparticles as carriers of various drugs and to find out what factors determine their main properties. PHA homopolymers and copolymers were examined, along with different drugs of varying molecular weight.
PHA specimens of two types were used: a homopolymer of 3-hydroxybutyrate (P3HB) and copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (P(3HB/3HV)) containing different percentages of hydroxyvalerate. Microparticles were prepared by the solvent evaporation technique, using double (water/oil) and triple (water/oil/water) emulsions. The influence of the preparation procedure on the yield, structure and size of microparticles prepared from PHA was examined here.
Results suggest that the major factors influencing the sizes of PHA microparticles are polymer solution concentration and the technique of emulsion micronization. Furthermore, the structure of the microparticle surface is determined by the chemical composition of the polymer and the type of surfactant. The diameters of prepared microparticles range between 10-200 nm and 50-100 μm. Investigation of the in vitro drug release behavior shows that total drug released from the microparticle into the medium increases with increasing 3-hydroxyvalerate fraction of P(P3HB/3HV) particles, mass concentration of the drug and porosity and with decreasing particle size. Factors influencing the properties of PHA microparticles have been determined in this study, and it has been shown that by varying the production parameters, one can prepare drug-loadable microparticles with different properties and regulate drug release rates.
The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and Program of the President of Russia for young Doctors of Sciences (Grant No *MD-3112.2012.4).*

P 11

DETERMINATION OF ACTIVITY SERUM PHOSPHOMONOESTERASES AFTER THE ADMINISTRATION BIODEGRADABLE POLYMER MICROPARTICLES *IN VIVO*

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Designing of controlled release drug delivery systems is a promising and rapidly development line of pharmacology. The microbial polyhydroxyalkanoates (PHAs) are aliphatic thermoplastic biopolyesters. PHAs are studied as a bioimplant material for tissue engineering due to its combined properties of adjustable mechanical properties, biocompatibility, biodegradability and non-cytotoxicity of its degraded products. Therefore the PHAs are great a biodegradable material for designing the controlled drug delivery systems.
The aim of this work is the designing of polymeric microparticles, studing of their characteristics and determining the activity of serum phosphomonoesterases (acid and alkaline phosphatases) due to their implantation *in vivo*.
Microparticles were prepared by the solvent evaporation technique using a double emulsion. Distribution of particle size and surface charge were investigated. Microparticles were received with a mean diameter 0,7±0,12 μm (intravenous administration) and 20±0,95 μm (intramuscular administration). Sterile microparticles were introduced to laboratory animals - adult female and male rat Wistar (220-240g).
The change of alkaline phosphatase activity in the experiment shown low inflammatory response of the organism on the first days after administration. And this change demonstrated process of vascularization at the end of the experiment. The activity of acid phosphatase of macrophages, as a marker of the intensity of the biodegradation of polymeric materials, was increased significantly during the experiment.
These results characterize the response to the introduction of PHB microparticles as local inflammation. In general, the studies establish that polyhydroxyalkanoates and their products have high medical and biological properties. Therefore this class can be recommended for creating a biodegradable polymer-controlled drug delivery systems.

The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and the Program of the President of Russia for young Doctors of Sciences (Grant No MD-3112.2012.4).

P 12

THE STUDY OF KINETICS OF OXIDATIVE POLYMERIZATION OF ANILINE FOR THE PURPOSE OF CREATION OF POLYANILINE-BASED BIOCOMPATIBLE MATERIALS

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Polaniline possesses a unique variety of properties which provide for the possibility of its application in different areas of medicine and biology. High chemical inertness and low toxicity of polyaniline make it possible to use it in manufacturing of products which can contact with blood. Moreover, hemocompatibility of polyaniline is determined by its structure, which made it necessary to study the kinetics of its polymerization.
The kinetics of oxidative polymerization of aniline initiated by ammonia peroxydisulfate in dilute aqueous solution was studied by potentiometric method. The amount of oxidizing agent was twice as much in respect to aniline. Since protons are s when oxidative polymerization of aniline takes place, the reaction monitoring was carried out by observing the change in pH of the reaction medium with time.
1.29 g (0.01 mol) of aniline were dissolved each in 50 ml of bidistilled water and placed in thermostat. Then 2.56g (0.0125 mol) of ammonia peroxydisulfate dissolved in 50 ml of bidistilled water and kept in thermostat for 30 minuets were mixed with the monomer solutions. The oxidative polymerization of aniline was carried out at 25, 30 and 35^{0}C respectively. The reaction was monitored by pH-meter (Ecotest-2000).
It was shown that in the process of oxidative polymerization of aniline autocatalysis takes place. It was determined that the rate of oxidative polymerization of aniline with ammonia peroxydisulfate is governed by equation: $-d[Ani]/dt=k_1[Ani]([Ox]_0-([Ani]_0-[Ani]))+ k_2([Ani]_0-[Ani])$
where: [Ani]-aniline concentration; [Ox] - ammonia peroxydisulfate concentration.
The kinetic coefficient of one-electron transfer from aniline molecule to peroxydisulfate ion (k_1) are 0.0152, 0.0488 and 0.157 l/(mol.sec) at 25, 35 and 45°C respectively. The energy of activation of one-electron transfer is 95.4 kJ/mol.

The kinetic coefficients of autocatalytical oxidation of aniline (k_2) are 7.2.10-3, 8.10-3 and 9.10-3 1/sec at 25, 30 and 35°C respectively. The energy of activation of autocatalytical oxidation of aniline is 7.2 kJ/mol and is a fictitious variable.

P 13

POLYPYRROLE AS A HEMOCOMPATIBLE MATERIAL

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Polypyrrole possesses a unique variety of properties which provide for the possibility of its application in different areas of medicine and biology. High chemical inertness and low toxicity of polypyrrole make it possible to use it in manufacturing of products which can contact with blood. Moreover, hemocompatibility of polypyrrole is determined by its structure, which made it necessary to study the kinetics of its polymerization. It was shown that in the process of oxidative polymerization of pyrrole autocatalysis takes place. It was determined that the rate of oxidative polymerization of pyrrole with ammonia peroxydisulfate is governed by equation:
-d[Pyr]/dt=k1[Pyr]([Ox]0–([Pyr]0-[Pyr]))+ k2([Pyr]0-[Pyr])[Pyr]
where: [Pyr]- pyrrole concentration; [Ox]- ammonia peroxydisulfate concentration.
The kinetic coefficient of one-electron transfer from pyrrole molecule to peroxydisulfate ion (k1) are 0.01, 0.017 and 0.03 l/(mol.sec) at 25, 30 and 35°C respectively. The energy of activation of one-electron transfer is 84 kJ/mol.
The kinetic coefficients of autocatalytical oxidation of pyrrole (k2) are 0.38, 0.2 and 0.13 l/(mol.sec) at 25, 30 and 35°C respectively. The energy of activation of autocatalytical oxidation of pyrrole is - 81кДж/моль and is a fictitious variable.
The dynamics of formation of water-insoluble polypyrrole sediment in the course of reactiont was controlled by measuring the optical density of reaction medium (turbidimetry). For this purpose, 1ml of pyrrole solution (0,067 g of pyrrole in 50 ml of bidistilled water) and 1 ml of ammonia peroxydisulfate solution (0,456 g in 50ml of bidistilled water) were mixed fast in a quartz cell at 25 C. The monitoring of polypyrrole sediment formation was carried out by measuring each 30 seconds the optical density at 590 nm of the reaction system.

P 14

BIOMEDICAL CONSTRUCTIONS IN THE FORM OF SCAFFOLDS OF THE PHA FOR THE TAKS OF CELL AND TISSUE ENGINEERING

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Recent advances in cellular and tissue engineering have gave big for developing innovative and effective biomedical technologies for repairing damaged tissues and organs, treatment of different severe human diseases. Among the materials developed and studied, polyhydroxyalkanoates (PHAs) - are biodegradable linear polyesters of microbiological origin - are very interesting materials for these purposes.
A series of different types of carriers (film, pressed scaffolds, volumetric forms-composites) received and investigated in the work. Used samples of homogeneous polymer 3-hydroxybutyric acid (P-3-HB) with the inclusion of 3-hydroxyvalerata (3 HV) 9,3 mol%.
A comparison of properties of the surface of polymeric carriers developed. Total porosity and moisture absorption estimated. The biocompatibility of the scaffolds and the ability to adhesion cultured cells showed on the example of fibroblast cultures line NIH 3T3.
It is established that the characterization of the surface of the samples depends significantly on the manufacturing techniques and the type of polymer matrix. The lowest rate registered in composite on the basis of PHB/collagen ($60^0 00^l \pm 1^0 50^l$); the highest - in pressed samples ($69°50^l \pm 1^0 30^l$). The composite matrix PHB/collagen (0,65 ± 0,12 cm^3/g) had the largest index of total porosity. While the pressed and film scaffolds, had the lowest similar values (0,14±0,023 cm^3/g; 0,2±0,016 cm^3/g).
The number of proliferating cells fibroblasts were more on all the samples of a composite PHB/collagen (500 x 10^3 cells) compared with samples from PHB. The initial concentration of attached cells on the composites was higher due to the hydrophilic surface of the hybrid scaffolds.
In General, the carry out research showed the possibility to obtain the carriers for the cultivation of cells on the volume of porous PGA/collagen scaffolds, pressed and film samples.

The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and the Program of the President of Russia for young Doctors of Sciences (Grant No MD-3112.2012.4).

P 15

POLYANILINE – POLY(N-VINYLPYRROLIDONE) COMPLEX AS AN ADVANCED MATERIAL IN MEDICINE AND BIOLOGY

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Due to its high inertness, electrical conductivity, and biocompatibility, polyaniline possesses a unique variety of properties. At the present time it was shown that polyaniline may be used for production of biosensors and underlayers for gene engineering. Polyaniline is also capable of forming complexes with DNA. Moreover, low solubility of polyaniline limits the possibility of its application. In the current work the formation of stable aqueous dispersions of polyaniline with water-soluble polymers, such as PVP and PVA, was demonstrated. The mechanisms of polymerization of aniline in PVP aqueous solutions were studied.
The kinetics of pyrrole oxidative polymerization in aqueous solution with ammonium peroxydisulfate was studied. The autocatalysis was found to be responsible for the acceleration of the reaction and the new mechanism of oxidative polymerization of pyrrole considering autocatalysis was proposed. The kinetic model of oxidative polymerization of pyrrole was developed and main parameters of this model were determined.
It was determined that the rate of oxidative polymerization of aniline with ammonia peroxydisulfate is governed by equation: $-d[Ani]/dt=k_1[Ani]([Ox]_0-([Ani]_0-[Ani]))+ k_2([Ani]_0-[Ani])$
where: [Ani]-aniline concentration; [Ox] - ammonia peroxydisulfate concentration.
The kinetic coefficient of one-electron transfer from aniline molecule to peroxydisulfate ion (k_1) are 0.0152, 0.0488 and 0.157 l/(mol.sec) at 25, 35 and 45°C respectively. The energy of activation of one-electron transfer is 95.4 kJ/mol.
The kinetic coefficients of autocatalytical oxidation of aniline (k_2) are 7.2.10-3, 8.10-3 and 9.10-3 1/sec at 25, 30 and 35°C respectively. The energy of activation of autocatalytical oxidation of aniline is 7.2 kJ/mol and is a fictitious variable.

P 16

SOME ASPECTS OF APPLICATION OF POLYPYRROLE – POLY(N-VINYLPYRROLIDONE) COMPLEX IN MEDICINE AND BIOLOGY

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Due to its high inertness, electrical conductivity, and biocompatibility, polypyrrole possesses a unique variety of properties. At the present time it was shown that polypyrrole may be used for production of biosensors, underlayers for gene engineering, and also for production of biocompatible materials. Moreover, low solubility of polypyrrole limits the possibility of its application. In the current work the formation of stable aqueous dispersions of polypyrrole with water-soluble polymers, such as PVP and PVA, was demonstrated. The mechanisms of polymerization of pyrrole in PVP and without PVP in aqueous solutions were studied.
0.067g (0.001 mol) of pyrrole were dissolved each in 50 ml of bidistilled water and placed in thermostat. Then 0.456g (0.002 mol) of ammonia peroxydisulfate dissolved in 50 ml of bidistilled water and kept in thermostat for 30 minuets were mixed with the monomer solutions. The oxidative polymerization of pyrrole was carried out at 25, 30 and 35^{0}C respectively. The reaction was monitored with pH-meter (Ecotest-2000).
The effect of autoacceleration in the course of pyrrole oxidation polymerization initiated by ammonium peroxydisulfate as a result of autocatalysis was established. A new mechanism of pyrrole oxidation polymerization describing the formation of charge transfer complex between protonated form of polypyrrole and monomer was proposed to explain the effect of autocatalysis. On this basis, the kinetic model of pyrrole oxidation polymerization was developed, which was found to be in agreement with experimental data up to high conversion of the monomer. Some parameters of this model, such as one-electron transfer and autocatalytic oxidation rate constants at various temperatures were determined and appropriate activation energies were found.

P 17

THE MICROSTRUCTURE OF POLYANILINE CHAIN AS A KEY FACTOR OF BIOCOMPATIBILITY

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In the present time more and more researches are focused on creation of biocompatible materials based on polyaniline. It was shown that biocompatibility of polyaniline is determined by aminobenzoic and quinodiimine fragments ratio. Aminobenzoic and quinodiimine fragments ratio was studied by means of UV-spectroscopy fo0r polyaniline, synthesized in different media. The influence of temperature, oxidizer molar excess, and monomer concentration on polyaniline chain fragment ratio was determined.
The kinetics of oxidative polymerization of aniline initiated by ammonia peroxydisulfate in dilute aqueous solution was studied by potentiometric method. The amount of oxidizing agent was twice as much in respect to aniline. Since protons are s when oxidative polymerization of aniline takes place, the reaction monitoring was carried out by observing the change in pH of the reaction medium with time.
1.29 g (0.01 mol) of aniline were dissolved each in 50 ml of bidistilled water and placed in thermostat. Then 2.56g (0.0125 mol) of ammonia peroxydisulfate dissolved in 50 ml of bidistilled water and kept in thermostat for 30 minuets were mixed with the monomer solutions. The oxidative polymerization of aniline was carried out at 25, 30 and 35^{0}C respectively. The reaction was monitored by pH-meter (Ecotest-2000).
The kinetic coefficient of one-electron transfer from aniline molecule to peroxydisulfate ion (k_1) are 0.0152, 0.0488 and 0.157 l/(mol.sec) at 25, 35 and 45°C respectively. The energy of activation of one-electron transfer is 95,4 kJ/mol.
The kinetic coefficients of autocatalytical oxidation of aniline (k_2) are 7.2.10-3, 8.10-3 and 9.10-3 1/sec at 25, 30 and 35°C respectively. The energy of activation of autocatalytical oxidation of aniline is 7.2 kJ/mol and is a fictitious variable.

P 18

SYNTHESIS OF 3-HYDROXYBUTYRATE-CO-3-HYDROXYHEXANOATE COPOLYMERS BY *RALSTONIA EUTROPHA*

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Polyhydroxyalkanoates (PHAs) are natural polyesters produced by numerous microorganisms under unbalanced growth conditions. PHAs can be used in packaging, agricultural, medical, veterinary and marine applications because they behave similarly to conventional thermoplastics with the advantage of complete biodegradation.
A copolymer of polyhydroxybutyraten (PHB) with monomer 3-hydroxyhexanoate attracts the attention of many researchers because of its better mechanical performance and faster biodegradation.
The aim of this work is to study the ability of the bacteria Ralstonia eutropha B5786 to synthesize 3-hydroxybutyrate-co-3-hydroxyhexanoate (poly(3HB-co-3HHx)) under autotrophic and heterotrophic conditions.
Under autotrophic conditions R. eutropha B5786 was grown with a limit of nitrogen. During the experiment a salt of hexanoic acid was added. Polymer yield at a single addition of hexanoic acid was higher (50% of dry biomass weight) compared with several portions addition (46% of dry biomass weight). The content of 3-HHx was 3 mol.%. Addition of several portions of hexanoic acid in the medium and increasing of the cultivation time increased the content of 3-HHx to 6 mol.% after the single addition of hexanoic acid and to 9 mol.% after the second addition. Under heterotrophic conditions acrylic acid was added (0.1, 0.5 and 1.0 g/l). It was shown that the proportion of 3-HHx in the copolymer increased from 9 mol.% to 51mol.%. At the same biomass yield decreased, but the polymer content in the cells was constant.
Thus, it was found that varying of the cultivation conditions and concentration of acrylic acid it is possible to obtain poly(3-HB-co-3-HHx), which contains 3-HHx from 3 mol.% to 50 mol.%.
The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and the Program of the President of Russia for young Doctors of Sciences (Grant No MD-3112.2012.4).

P 19

HIGH-TEMPERATURE METHOD OF SYNTHESIS OF INORGANIC BIOCOMPATIBLE MATERIALS BASED ON YTTRIUM, ZIRCONIUM , AND CHROME SALTS

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It was determined that the high-temperature pyrolysis of yttrium, zirconium, and chrome salts with various reducing agents in silicon oxide matrix allows for obtaining of high-duty biocompatible materials. The kinetics of high-temperature processes is studied by means of thermogravimetric analysis.
It was shown that the impregnation of silicon oxide-based composite materials, reinforced with asbestos, in yttrium salts allows for improvement of thermoresistance from 1730^{0}C to 2100^{0}C. It was determined that the induction of yttrium nitrate with pyrolysis at 900^{0}C allows for reinforcement of silicon oxide composite materials.
Similar results were achieved when zirconium dioxide was induced in silicon dioxide matrix. The induction of zirconium dioxide allowed for achieving two-fold reinforcement of the composite material at 1000^{0}C as compared with the initial sample. Thermoresistance of the obtained composite material also increased up to 2300^{0}C.

P 20

CHARACTERISTICS OF PROTEINS SYNTHESIZED BY HYDROGEN-OXIDIZING MICROORGANISMS

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Protein is the most unavailable component of human nutrition, and now global demand for protein are not fully satisfied. Actual direction is attraction of new alternative sources of dietary protein, one of which is a protein of microorganisms. Promising outlook for hydrogen-oxidizing bacteria in comparison with other developed protein producers depends on high content of amino acids complete protein (to 60-70%).
The object of study hydrogen bacteria Alcaligenes eutrophus Z1 and Ralstonia eutropha B5786 and the CO-resistant strain of carboxydobacterium Seliberia carboxydohydrogena Z1062.
The total protein content in the biomass, its fraction and amino acid composition, digestibility by proteolytic enzymes in vitro were analyzed.
Cultivation of bacteria was performed in flow mode using an automated complex fermentation BioFlo 110, «New Brunswic» (USA). The amino acids in the mixture were then analyzed by using Automatical Amino Acid Analyser KLA-38 (Chitachi, Japan). Separation of protein fractions in the study and their fractional composition was performed in alkaline and salt solutions. Availability of protein fractions was determined by the method of Pokrovsky-Ertanova using proteolytic enzymes.
The studied proteins contain essential amino acids (their content in the total fraction up to 40%). The amount of essential amino acids in all studied strains exceeded the content of essential amino acids in grain (more than 10%), and was close to that in casein.
The fractional composition of bacterial proteins differs from conventional proteins very much. Fractions I and II (the most available to the digestive enzymes) of meat protein are about 80%. On the contrary, fractions I and II of hydrogen-oxidizing bacteria proteins are about only 50%. Based on a number of significant parameters characterizing the biological value of a product, the proteins of hydrogen-oxidizing microorganisms have been found to occupy an intermediate position between traditional animal and plant proteins. The high total protein in biomass of these microorganisms, their complete amino acid content, and availability to proteolytic enzymes allow for us to consider these microorganisms as potential protein producers.
The study was supported by the project initiated by the Government of the Russian Federation (Decree No. 220 of 09.04.2010) for governmental support of scientific research conducted under the guidance of leading scientists at Russian institutions of higher learning (Agreement No. 11.G34.31.0013) and the Program of the President of Russia for young Doctors of Sciences (Grant No MD-3112.2012.4).

P 21

MICROENCAPSULATED MULTICELLULAR TUMOR SPHEROIDS AS A 3D MODEL TO STUDY CYTOTOXICITY OF NOVEL DOXORUBICIN DERIVATIVES

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Doxorubicin (DOX) is widely used in cancer chemotherapy from the 80s of the last century, though, as a majority of other anticancer drugs, it has low selectivity. It was previously shown that due to ability to activate apoptosis, some fatty acids possess selective antitumor effect. It is also known that these acids form stable complexes with albumin circulating in blood. Modification of chemotherapeutical agents by fatty acids could provide their ability of form complexes accumulating in tumor tissue as a result of passive transport.
The aim of this research is to study cytotoxicity of DOX derivatives modified with palmitic acid, in two *in vitro* models, e.g. monolayer culture (2D) and multicellular tumor spheroids (MTS) which can be considered as 3D model. Moreover, DOX-5-fluorouracil (5FU) conjugates were prepared and their cytotoxicity for DOX-resistant tumor cell lines was evaluated.
Human cervix adenocarcinoma cells HeLa and two human breast adenocarcinoma cell lines (MCF-7 and DOX-resistant MCF-7/DXR cells) were used in this research. MTS were generated by long-term cultivation of cells in polyelectrolyte alginate-oligochitosan microcapsules for 2-3 weeks, as previously described [Zaytseva-Zotova et al. (2011) J Biomed Mater Res B Appl Biomater. 97(2):255-62]. Cell viability was calculated by MTT assay in 24, 48 and 72 hours after incubation with DOX samples. It was shown that the conjugates with palmitic acid were more effective to HeLa and MCF-7 cells in comparison with DOX-FU5. However, DOX-FU5 activity remained at the same level in the case of DOX-resistant cells, whereas the activity of the other DOX derivatives decreased. It was also demonstrated that in the case of MTS the higher doses of all DOX derivatives were needed to achieve the effect similar to this in the monolayer culture (2D model).

P 22

STUDY OF CYTOTOXICITY OF MACROPOROUS SCAFFOLDS BASED ON POLY(VINYL ALCOHOL) MODIFIED WITH 2-HYDROXYETHYL METHACRYLATE

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Hydrogels are widely used as scaffolds for tissue engineering because of their biocompatibility and high water content which is close to that of human tissue. A porous structure of hydrogels enables rapid nutrient and oxygen transfer and provides high surface for cell attachment, growth and vascularization.
Hydrogels based on poly(vinyl alcohol) (PVA) are promising systems for biomedical applications, in particular for tissue engineering. One of the most widely used PVA hydrogels are physical cryogels. However, physical PVA cryogels have rather low mechanical and thermal stability, and additional methods which commonly deal with the use of toxic cross-linking agents or hard radiation are needed for structure stabilization. Formation of mechanically and thermally stable PVA hydrogels can be achieved by chemical cross-linking, e.g. by introduction of unsaturated methacrylic groups. Hydrogels based on acrylated PVA (Acr-PVA) have unique combination of high porosity with adequate mechanical strength. Moreover, for synthesis of these cross-linked hydrogels aqueous solvents are used which make them suitable for different biomedical applications.
However, intrinsically pure PVA cannot provide good cell adhesion because of extremely hydrophilic nature. In order to increase hydrophobic properties of PVA, and thereby to enhance cell attachment to the matrix, Acr-PVA was additionally modified with 2-hydroxyethyl methacrylate (HEMA).
In this research we aimed to evaluate *in vitro* cytotoxicity of hydrogels based on PVA modified with glycidyl methacrylate and HEMA (10-90% w/w).
The cytotoxicity of the hydrogels was studied by MTT-test in extraction and direct contact tests. Mouse fibroblasts L929 were used as model cells. For the extraction test, hydrogels were incubated with cell cultivation media for 24 hs. Then cells were cultivated with the extracts and after 3 days cell viability was measured. For the direct contact test, the hydrogels were kept in contact with the cell monolayer for 24 hs. To study cell growth and proliferation the cells were directly cultured on the PVA-HEMA hydrogels for 7 days.

The obtained results confirmed that modification of hydrogels with HEMA didn't lead to any significant cytotoxicity and promoted cell growth and proliferation. Cell viability increased with enhancement of HEMA content in the polymer matrix from 10 to 90 %.
Thus, the modifications of Acr-PVA hydrogels with HEMA allowed to promote cell growth and proliferation, and therefore could be considered as promising scaffolds for tissue engineering.

P 23

MACROPOROUS POLYMER HYDROGELS WITH CHARGED SURFACE FOR THE CELL CULTIVATING

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Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. They are commonly used in clinical practice and experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine, diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions. Macroporous polymer hydrogels, which characterises by an interconnected porous system, are known to be promising materials for the tissue engineering due to their ability to support a cell growing and promotion the diffusion of nutrients and metabolites inside and outside of cells, respectively.
The main aim of this research was in creating scaffolds with the charged surface which provided the most comfort environmental for the cell proliferation and growing. Obtained material was based on a copolymer of the modified poly(vinyl alcohol) with the diethylaminoethyl methacrylate for the positive charge and the acrylic acid for the negative charge. Materials were made in frozen water solutions; reaction took place at temperature range from -5 to -20 with the presence of radical polymerisation initiation system. Derive materials contains charged groups in amount from 1 mol.% to 20 mol.%. The relation between yield and different characteristics of reaction mixture were investigated during this work.
On the obtained hydrogels was cultivated L-929 mouse fibroblasts cell line and MSC line. It was shown that the optimal amount of the charged groups for the cell growing for the L929 cell line is 2,5 mol% and for MSC is 12,5 mol%.

P 24

TRANSITION METAL COMPLEXES WITH THE AMPHIPHILIC POLY-N-VINYLPYRROLIDONE

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Polymer complexes of transition metals are quite interesting and promising compounds having a number of properties: low toxicity, ability to stimulate production of interferon antiviral activity, etc. The use of such compounds in pharmacology and medicine will provide new drugs and expand the range of applicability of existing funds.
Consider the question of production and the possibility of using transition metal complexes (in particular whith salts of Pd^{2+}, Mn^{2+} и Ce^{4+}). Amphiphilic polymers prepared by free radical polymerization of N-vinylpyrrolidone in the solution whith an initiator and a transmitter circuit. Determination of the molecular weight of polymers produced by the reverse of the redox titration. Further, polymers were obtained by modifications to the introduction of side chain carboxyl and primary amine groups. For complexes used aqueous solutions of salts of transition metals. All complexes were subjected to a thorough cleaning to remove unbound metal ions.
In the course of the study were obtained dependence the polymer molecular weight on different factors: polymerization temperature, time, amount of initiator and transmitter circuit. Optimal conditions of synthesis were obtained. It is also considered the possibility of using polymeric complexes with ions Mn^{2+} and Ce^{4+} for biodegradable films. Metal complexes with Pd^{2+} ions are studied for the presence of interferon-stimulating and antiviral activity

P 25

DEVELOPMENT OF NOVEL POLYMERS AND DOSAGE FORMS ON THEIR BASIS

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A lot of low-molecular drugs and other biologically active substances are quickly eliminated from organism by different defensive mechanisms or metabolized as they frequently possess poor solubility in aqueous media and low capability to penetrate through cells membranes. Such problem of preparations prolonged activity can be solved and poor solubility effect can be greatly reduced by incorporating biologically active substances in the nanocapsules, for example, micelles of amphiphilic polymers, which can provide targeted delivery of drugs to the disease hotbed and their prolonged and controlled release.
During the present investigation nanoparticles were obtained on the basis of amphiphilic N-vinylpyrrolidone polymers containing a fragment of a hydrophilic polymer chain, as well as a hydrophobic long-chain aliphatic fragment. Were obtained and investigated polymers with different length of hydrophobic fragments. Polymeric nanoparticles containing biologically active substances in its core were obtained by dialysis and emulsion methods. The felodipine drug was used as a model substance for encapsulating in polymeric nanoparticles. It was found that the efficiency of the inclusion of felodipine in the polymeric nanoparticles obtained by emulsion method, significantly higher than that of particles obtained by the method of dialysis. The efficiency of the inclusion varies from 0.4 to 2.5% for the dialysis method, and from 4 to 11% for the emulsion method. The most effective encapsulation is observed at high values of polymer / felodipine ratio and for low concentration of felodipine in the initial mixture.
Thus, it becomes apparent that the production of new biocompatible amphiphilic polymers with optimal properties and the development of biologically active substances delivery systems on their basis is one of the most promising areas of new highly effective products for medicine, veterinary, biotechnology and agriculture.

P 26

POROUS HYDROGELS ON THE BASIS OF MODIFIED STARCH AND PVA

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Polymeric hydrogels on the basis of natural polymers owing to their good properties (high biocompatibility, high swelling ability in water solutions, ability to full biodegradation) are applied as implants in medicine, substrates in cellular engineering etc. The materials in terms of starch are very perspective due to their high biodegradation rate, but they are brittle and have not enough mechanical resistance. The problem of creation new hydrogels with different additives in order to get materials with improved properties still faces to the scientists.
As objects for creation materials with the different biodegradation speeds we had chosen 2-hydroxyethylstarch and modified PVA as additive. We had been synthesized series of porous polymeric hydrogels under low temperature with 47.43%, 23.12%, 13.07%, 7.58% content of 2-hydroxyethylstarch. Porous size of obtained hydrogels is 70-100 micron in average.
The biological tests have shown absence of toxicity and high biocompatibility of developed hydrogel materials. It has been shown that at contact to organism living tissues the synthesized hydrogels cause inflammatory reaction with formation of a granulation tissue in 1 and 3 week, did not cause inflammatory reaction in 5 week and 6,5 week and completely degraded, being replaced with organism tissues in 6,5 week. Speed of biodegradation was defined by character of porous structure and quantitative composition of polymeric hydrogels.

P 27

PLANT GROWTH REGULATORS ENCAPSULATED IN NANOSIZE PARTICLES OF AMPHYFILIC POLY-N-VINYLPYRROLIDONE

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Natural phytohormones and their synthetic analogues are one of the most important groups of plant growth regulators used in agriculture. Their practical application is however hindered by a number of obstacles, low solubility

in water and the need of precise dosage in order to prevent growth hampering action to name among the most influential ones. Immobilization on polymers for the purpose to obtain a controlled release system is a promising way to compensate for these flaws.
The use of nanosize particles of amphiphilyc polymer was suggested to implement this approach. The selected polymer carrier was previously developed for immobilization and internal delivery of water insoluble drugs. More accurately it was a water soluble carbon-chain polymer modified by the hydrophobic stearyl fragments that forms the aggregates in water where immobilized biologically active substance is encapsulated.
The plant growth regulators selected for immobilization were chosen from the two principal classes of phytohormones – the auxins and cytokinins. The former were various aryl- and aryloxy- carboxylic acids like 3-indolebutyric acid and other analogues of natural hormones. The later were regulators of adenine-type cytokinins like 6-benzylaminopurine.
Amphyphilc polymers based on polyacrylic acid, polyacrylamide and poly-N-vinylpyrrolidone of different molecular weight were compared. The most stable particles that showed a suitable release rate were obtained with poly-N-vinylpyrrolidone polymers with molecular weight of 12000 (approx.).
The correlation of molecular weight with particle size was revealed through dynamic light scattering study. The influence of pH on the inclusion degree was investigated.
Controlled release behaviour of the samples was confirmed by investigating their hydrolysis rate and its influence on the plant growth and development.

P 28

RADIATION CROSSLINKING OF POLYVINYL ALCOHOL MODIFIED WITH GLYCIDYL METHACRYLATE

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The researchers involved in the development of new biomaterials have paid great attention to polymeric hydrogels due to their biocompatibility, excellent mechanical and elastic properties that are close to the properties of living tissues, and a number of other unique characteristics.
Polymeric hydrogels can be obtained by copolymerization of low-molecular weight monomers or cross-linking of water-soluble polymers initiated, for example, by gamma radiation. The process initiated by gamma radiation ensures fine control of the crosslinking density and the preparation of polymeric hydrogels free of substance initiators, which is the most important advantage in further medical applications.
The objective of this work is to study radiation crosslinking of the modified polyvinyl alcohol (PVA) and the properties of the resulting hydrogel.
Polyvinyl alcohol modified with glycidyl methacrylate (GMA) is a PVA polymer chain containing side groups with multiple GMA bonds, which can polymerize by a radical mechanism when exposed to gamma radiation. When the double bonds of the same PVA chain interact, the resulting cyclic structures have different lengths, and thus, a possibility for insoluble gel formation is eliminated. The interaction of the double bonds localized at different PVA macromolecules initially brings to the formation of the branched and then three-dimensional cross-linked structures. The formation of the crosslinked structures was assessed by the content of the polymer gel fraction.
The studies of the PVA copolymer cross-linking during radiation exposure showed a typical S-shaped kinetic dependence, which is characteristic of polymerizing bi-and polyfunctional (meth) acrylic monomers. With increasing temperature the rate of cross-linking naturally increases, but at a lower temperature a higher content of gel fraction is achieved.
Irradiation of the original PVA solution under the same conditions (temperature and concentration) does not lead to the formation of crosslinked structures. Moreover, the irradiated system becomes a solution of lower viscosity, indicating the destruction of the original PVA chains.
We were unable to reach the content of the gel fraction higher than 60%. It could be due to the presence of the PVA monomer units, which do not contain GMA. Another possible reason could be related to the dynamic equilibrium, which is established between the processes of double bond cross-linking and PVA chain destruction in the experimental conditions.
The yield of the crosslinked polymer (content of gel fraction) was studied depending on the concentration of the modified PVA in the reaction system. It was shown that cross-linked hydrogel was not formed at the concentrations of the modified PVA lower than ~ 2.5 wt. %. At the concentrations ranging from 2.5 to 3.5 wt. % a sharp increase in the yield of the cross-linked polymer (gel-fraction content reached about 40%) was observed, and a further increase in the concentration had practically no effect on the crosslinking yield.

A differential scanning calorimetry was used to study phase transitions of the water immobilized in hydrogels. It is established that water is present in PVA gels at least in two different states: "bound" and "free", where a fraction of the "bound" water is 50-70% regardless of the gel fraction content.
Thus, in this work a possibility of preparing PVA gels by the radiation-chemical method is described and the properties of these three-dimensional cross-linked hydrogels are studied.

P 29

NANOSTRUCTURED POWDERS FOR MATERIALS WITH BIOLOGICAL AND MEDICAL APPLICATIONS – EFFECTIVE PRODUCTION TECHNOLOGIES

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A lot of materials for a wide range of medical and biological applications require nanostructured powder as a raw material for their production. To name several of them: - RE oxides and aluminates nanopowders for making of transparent ceramics, which is used as detector material for computed tomography [1], as well as for making ceramics for laser, which are widely used in surgery; - alumina and RE stabilized zirconia powders for dental ceramics [2]; - oxide powders for bioceramics including orthopedic implants [3] and artificial bones. These applications could be supplemented with ongoing investigations on antimicrobial and sunscreen properties of oxide nanoparticles.
All these applications are quite different, although all of them require high quality powder material of high purity in relatively large quantities. Laboratory techniques, such as organometallic aerosol pyrolysis and combustion synthesis could be not appropriate to these purposes because of low throughput. This means, that reliable production technologies are required, which yield the high quality powder and could be implemented in semi-industrial and industrial scales at the same time.

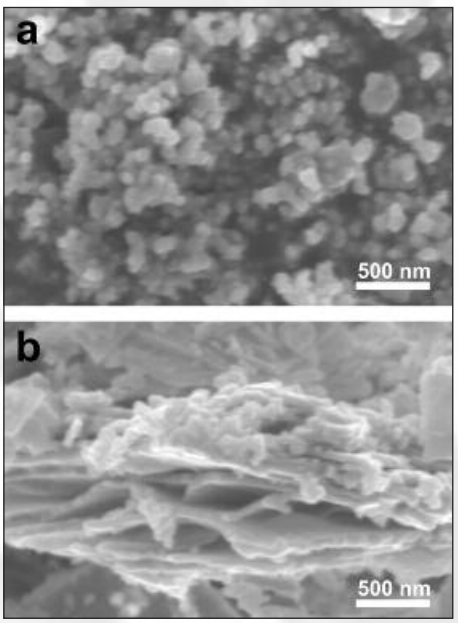

Fig. 1. Precipitated and annealed Y_2O_3 powder: a) particles morphology, b) plates morphology

Here we report our work on the development of technologically beneficial approaches to production of nanostructured metal oxide powders, including RE_2O_3, Al_2O_3, $RE_3Al_5O_{12}$, etc., in pure form for possible construction materials applications and in doped form for possible functional materials applications. The whole production process includes compound purification (usually, in a form of solution), solid pre-powder synthesis and calcination, leading to an oxide powder formation.
We consider a precipitation technique as one of the most applicable for the stated purpose, as it allows to obtain chemically clean powders and could be scaled up easily. It suits well to the RE_2O_3 and $RE_3Al_5O_{12}$ powders synthesis. Choice of the precipitant and the precipitating conditions (pH, stirring regime, solutions concentrations) allow to obtain nanostructured powders with different morphologies; e.g. Fig. 1 presents two different morphologies of Y_2O_3 oxide powder, precipitated with NH_4HCO_3 at different stirring conditions and solutions concentrations. Another technologically interesting approach is an alkoxide method, particularly suitable for Al_2O_3 and ZrO_2 extra-pure nanopowders synthesis.
The described techniques were successfully tested in semi-industrial reaction vessels.

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P 30

POLYMER-PROTECTED METAL NANOPARTICLES,IMMOBILIZED IN HYDROGELS

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Metal nanoparticles may be stabilized either by linear polymers or by hydrogels. Both methods have some scarcities:
1. Colloidal metal nanoparticles solutions have tendency to instability and precipitation
2. Metal nanoparticles are lightly removed from hydrogels volume.
It is suggested to use the combination of these two approaches: synthesis of metal nanoparticles, stabilized by linear polymers and then its immobilization into volume of hydrogels. Nanoparticles of palladium, gold and silver, protected by polyvinylpyrrolidone, polyvinylalcohol, polyethylene imine and polyacrylic acid were immobilized into polyacrylamide and polyisopropylacrylamide hydrogels matrix. It was shown that in this case the stability of such systems remarkable increase.

P 31

IDENTIFICATION OF NEW SYNTHETIC STIMULANTS IN HAIR SAMPLES BY PFIA, GC-MS AND HPLC-MS/MS METHODS

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At the present time there is sharp increase in illicit synthetic amphetamine-type stimulants: methylenedioxypyrovalerone (MDPV), fluorometilpiperazine, mephedrone, methilone, their analogs and homologs, as well as synthetic cannabinoids - the components of smoking mixtures. Identification of these compounds is complicated by absence of PFIA kits, standard samples, mass-spectra and retention parameters. In cooperation with forensic laboratories there have been developed to replenish mass-spectra libraries (with locked retention times), carried out testing and calibration of PFIA kits for these groups. Methods of SPE and liquid/ liquid extraction urine samples, organs and tissues for PFIA, GC-MS and HPLC-MS/MS indentification have beed developed. Prior analysis have been made with "Narcostop" kits (produced by "Osiris-C") and PFIA. Agilent 7890 (7820)-5975 was used for GC-MS, Agilent 1200-6460 for HPLC-MS/MS.
The process of SPE purification has been optimized for identification of stimulants in hair samples. Hair samples from corpses and from living persons (20-100mg), washed from impurities, were expose to alkaline (5M NaOH), acid (5M HCL) and enzymatic (β-glucuronidase pH 4.6-7) hydrolysis. Optimal results have been obtained while using enzymatic hydrolysis with pH 6, target compound/matrix ratio was worse when using acid hydrolisis and alkaline hydrolisis led to loss of the target substance. Acquired eluates have been preliminary analyzed by PFIA, the results have been confirmed by GC-MS and HPLC-MS/MS.

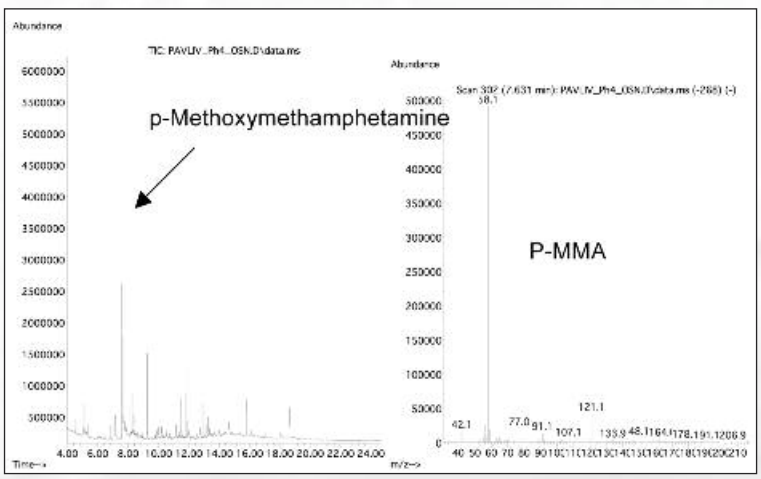

Figure 1. p- Methoxymethamphetamine in corpse hair (GC-MS-SCAN), enzymatic hydrolysis pH 4, SPE Bond Elute Sertify (50 mg hair used).

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APPLICATION OF CHITOSAN AND ITS MODIFIED FORMS FOR CREATION OF WOUND HEALING COATINGS

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Chitosan as a natural biopolymer is the ideal basis for a wound coverings. Chitosan's properties are: biocompatibility, antimicrobial action, non-toxic, forms fiber and film and can easily decompose. We are first to develop film biomaterials based on chitosan and chondroitin sulfate-protein complex (ChitCNPC) and the technology of its production. It is developed for the treatment of microbial destruction of the skin of an aquaculture fishes, which are contained mostly in adverse growing and transportation conditions. Wound healing ability of biomaterials ChitCNPC film was examined for aquaculture sturgeons. It is established that the application of biomaterials based on chitosan and chondroitin sulfate-protein complex on the affected areas of fish skin promotes healing of wounds and active skin regeneration. Thus corrosive medicines and disinfectant baths which are often used in aquaculture, as well as sophisticated equipment, was not used. It is promising is to get the film wound coverings for veterinary and medicine use, based on chitosan derivatives which were synthesized using oligo- (ethylene oxide) as a modifier, functionalized by introducing sulfo- and carboxyl groups. These modifiers are attached to amino- groups of chitosan salt bonds, but in contrast to acetic acid, the most commonly used to convert polymer in a water-soluble condition, allow to achieve the result using a significantly of its amount. Chitosan oligo- (ethylene oxide) sulfonate is dissolved in water at a degree of substitution of 0.75-0.8 and chitosan carboxyoligo- (ethylene oxide) sulfonate does it at a degree of substitution of 0.4-0.5. The absence of an excess of acidic modifier solution provides the ability to obtain neutral solutions, which is important for the solution of practical problems. The availability of new derivatives of chitosan oligo (ethylene oxide) flexible side chains attached to their high viscosity provides good elastic properties for the films. We obtained films from 2% aqueous solutions of chitosan carboxy- and oligo- (ethylene oxide) sulfonates and investigated their deformation and strength properties. The resulting films thickness are 130 to 200 microns, films are transparent and have high elastic and plastic properties (~ 200-250 %) and of sufficient strength (20-40 MPa) for use as a wound coverings. The strength of the films increases with decreasing modifier content and the presence there of two acid groups. Thus, obtaining a wide range of chitosan modifications and its use in combination with other biologically active substances, including chondroitin sulfate-protein complex, allows you to create film coatings with different physical-chemical properties, which leads to their wide application in various fields of medicine and veterinary.

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NATURAL BIOPOLYMERS - CARRAGEENANS: THEIR RECEIVING FROM RED ALGAE GENUS OF *KAPPAPHYCUS* AND *EUCHEUMA* CULTIVATED IN THE COASTAL AREA OF SOUTH VIETNAM

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Sulfated polysaccharides – carrageenans as a natural of biopolymers, widely used in the food industry as well as in medicine, biotechnology, engineering, etc. sectors of the economy. We've researched 20 samples *Kappaphycus alvarezii*, *Kappaphycus striatum* and *Eucheuma denticulatum*. Algae grew in the different times and seasons in the coastal area of South Vietnam: Khanh Hoi, Nhon, Phuong Cu, Cam Ranh. Red algae of *K. striatum* species was represented variations forms, it is of Sacol green and Sacol brown. Was supposed that they have differentiate not only in color talloms, but also by the properties of carrageenans. On the results of studying chemical composition of red algae-carrageenophytes and physicochemical properties of their carrageenans, it is established that seasonal variation is the major factor influencing on quality of kappa-carrageenan, obtained from cultivated algae genus *Kappaphycus*. Regimes of extracting, precipitating and pressing native carrageenan from *Kappaphycus* and *Eucheuma* were established with degree of extracting reached to 95 %, which maintain natural gel strength up to 900 g/cm^2 and are able to manufacture κ - and ι - carrageenans in one cycle of processing line. A technological scheme of k-carrageenan obtaining from red algae genus *Kappaphycus* and ι- carrageenan from *E.denticulatum*, cultivated during 60 days in different seasons, was developed.

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STABILIZATION OF GLUTATHIONE PEROXIDASE 1 AS APPROACH TO OBTAIN THE ANTIOXIDANT PREPARATION

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All cell forms are support "redox status" of the organism by means of antioxidant enzymes. Malfunction of this status is elevated increasing of toxic reactive oxygen forms such as peroxides and free radicals. As a result of reactive oxygen species action such important components of the cell as lipids and DNA are oxidized. In human organism, oxidative stress is a cause or an important component of many serious diseases such as atherosclerosis, hypertension, Alzheimer's and Parkinson's, diabetes, stroke, and is a component of the aging process.
Glutathione peroxidase is one of the most important enzymes which protect cells from reactive oxygen forms. Glutathione peroxidases catalyze reduction of lipid peroxides to corresponding alcohols and recovery of hydrogen peroxide to water. Glutathione peroxidase type 1 (GPx1) is the most abundant form of the enzyme, it was detected in the cytoplasm of all mammalian tissues, hydrogen peroxide is the substrate of GPx1.
In this regard, it becomes topical the application of antioxidant drugs based on the enzyme glutathione peroxidase in medical practice.The purpose of this work was to obtain and study the properties of mixtures of glutathione peroxidase and polyelectrolytes, which are often used to stabilize and improve the catalytic properties of enzymes.
Optimal conditions for measuring glutathione peroxidase 1 activity were found. The comparison of the native enzyme stability and that of its mixtures with polyelectrolytes of different nature (polyacrylic acids 5 and 240 kDa, polylysines 5.2, 9.6 and 55.2 kDa, polylysine and polyethylene glycol block copolymer 6.6 kDa, polyethyleneimine and polyethylene glycol block copolymer 12.6 kDa) was carried out at pH 8.0 after two days of incubation at 37°C. The stabilizing effect is achieved by addition of polyacrylic acid 5.2 kDa (residual activity is about 30% from the original, while the native enzyme loses its activity up to 7%) and polyethyleneimine and polyethylene glycol block copolymer 12.6 kDa (residual activity is about 50% from the initial, whereas the native enzyme loses its activity up to 12%), whose effectiveness depends on the ionic strength of the solution. The reasons for the observed phenomena are discussed.
Investigations were supported by Russian Ministry of Science and Education (grant No 11.G34.31.0004).

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POLYIONIC COMPLEXES FOR IMPROVEMENT OF PROPERTIES OF LYSK-THE ENZYME LYSING CELL WALLS OF STAPHYLOCOCCUS AUREUS

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Within last 10 years the increase in quantity of the diseases caused by staphylococci, is observed. Staphylococcus aureus is especially dangerous, as 90% of its strains are steady against action of antibiotics, for example, such as methicillin and vancomycin. The death rate among the patients infected methicillin-resistant Staphylococcus aureus, makes 31 % [1-3]. Bacteriolytic enzymes are biologically active substances which can be considered as adequate alternative to antibiotics. These enzymes are produced by bacteriophages in the course of them lytic cycles and are responsible for destruction (lysis) of cell walls of bacteria. Their mechanism of action is based on hydrolysis of chemical bonds in peptidoglycan, the important component of cell walls of bacteria. The recombinant bacteriolytic enzyme LysK was isolated in 2005. It effectively lyses cells of methicillin-resistant and vancomycin-resistant strains of Staphylococcus aureus [4].
It is necessary to notice, that the enzyme LysK is insufficiently stable in the conditions of storage (temperature 4-22°C) and functioning (temperature 37°C). The most perspective way of improvement of stability of the enzyme consists in addition to it of polymeric substances of the cationic nature. They help LysK to support catalytically active conformation in time, and also can promote interaction strengthening between the enzyme and a substratum.
In the given work influence of polyethyleneimine-poly(ethylene glycol) block copolymer (PEI-PEG) 12.6 kDa on LysK activity and stability is investigated at different concentration of a block copolymer (1 - 100 multiple excess on mole in relation to the enzyme) and temperatures (4, 22, 37°C). Interaction of LysK with PEI-PEG also has been character-

ized by method of the infra-red spectroscopy. Character of the received laws and their reasons are discussed.

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PROPERTIES OF THE PHOTOGRAPHIC GELATIN AND EDIBLE GELATIN AS AN ALTERNATIVE TO PHOTOGRAPHIC

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Investigated a possibility to use an edible gelatin in technology of manufacturing of light-sensitive materials as an alternative to photographic gelatin.
Studied a molecular – weight composition of gelatin (MWC). Found that the gelatin characterized by polydispersity, the main components of the gelatin are α, β-, and γ-chain (the last two components are cross-linked by chemical bonds double or triple α-chains) and their fragments. Polypeptide chains of different lengths have different charges, different pI, are differentiated by their ability to restore the three-helix collagen domains. MWC of gelatin depends on raw materials and technologies of manufacturing, and its effect on the composition stronger.
Examined dependence of the photographic properties of light-sensitive materials from molecular weight composition of gelatin (MWC). Demonstrated dependence of chemical sensitization rate, attaining of maximum photographic performance, as well as physico-mechanical properties of the photographic emulsion layers from molecular weight composition (MWC) of gelatins.
Studied variation of sensitometric characteristics of photographic emulsion on the properties of the gelatin, and depending on the basic components introduced into the emulsion on the stage of chemical sensitization. It is shown that a number of properties of edible gelatin correspond to the inert photographic gelatin.
The photographic emulsion, synthesized on edible gelatin, has a high photographic fogging ability during the chemical sensitization in the presence of gold salts, which indicates the presence in gelatin a large number of reducing impurities has a high photographic fogging ability. Demonstrated the possibility of removing a fog during the chemical sensitization of the emulsion by gold salts with sodium benzenesulfinate. At the same time achieved sensitometric characteristics similar to inert photographic gelatin, except of lower values of contrast ratio.

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DEVELOPMENT OF A TECHNIQUE OF POLARIZATION FLUORESCENCE IMMUNOASSAY FOR THE DETERMINATION OF FLUOROQUINOLONES IN FOOD

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Currently, fluoroquinolones (FQ) are widely used in veterinary medicine. 90% of all registered veterinary medicines on the basis of FQ accounts for enrofloxacin (ENR). Consumption of food contaminated with this drug can cause allergic reactions in humans. It is also important to note that different ENR pronounced postantibiotic effect is due to the active metabolite ciprofloxacin (CIP), which is mainly applied in medicine. In this connection, accumulation of these FQ in human organism may cause the appearance of resistant strains of pathogenic microorganisms. Therefore it is important to monitor the content of FQ in food. In most countries have adopted regulations to ensure food safety for the health of the consumer, which set acceptable levels of chemical pollutants such as FQ. For example, in the EU and Russia, MRLs for the content of the sum of fluoroquinolones (CIP + ENR + NOR + OLF) in the meat was set at 100-300 mg/kg, and in the milk of 100 mg/l.
The aim of this work was to develop method of polarization immunoassay for the determination of fluoroquinolones in food of animal origin.
We synthesized conjugates of fluoroquinolones (ENR, CIP, OLF, NOR, etc.) with bovine serum albumin (BSA) and flu-

oresceinisothiocyanate, a modified carbodiimide method. Conjugates with proteins (Ag) was used to immunize rabbits to produce polyclonal antibodies (Ab). Immunization was performed several times with monthly intervals with small doses of Ag (100 mg/rabbit) intradermally in the back. Blood was collected 7 days after injection. Sera were mixed with glycerol (1:1, v/v) and stored at minus 20 ° C and then tested for binding with different tracers (conjugates with fluoroquinolone derivatives of fluorescein) by fluorescence polarization immunoassay method (FPIA) to select the optimal combinations of immunoreagents (tracer + antibody). As a result, we chose conditions for FPIA setting (selected optimal concentrations of tracer and antibody, the working buffer), allowing to determine the fluoroquinolones in solutions in the range 1-1000 mg/l. Also, the developed method was optimized for the analysis of real objects. Test for the opening was performed, analytical characteristics for NOR, CIP, ENR and OFL was determined. The percentage of opening was 90-120%.
Thus, the immunoreagent were obtained and with their help FPIA technique was developed. This technique makes it possible to determine the fluoroquinolones in the solution, starting with 1 mg/l, and it can be used to create a diagnostic test systems. You can also determine the residual amounts of fluoroquinolones in samples of animal products with the help of the developed technique.

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ULTRATHIN FILMS WITH SYNTHETIC AND NATURAL IONOPHORES AS CHEMOSENSORING MATERIALS

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The preparation and study of polymer films with synthetic and natural ionophores is a rapidly growing field at the interfaces of polymers and colloids, ecology and analytics, animal and human medicine, bio- and nanotechnology. There are some publication, concerning the behaviour of mixed monolayers of peptide-ionophore (such as valinomycin, gramicidin, etc.) with lipids or polymers at the surface of various aqueous salt subphases. The study of such three-component systems (ionophore, lipid and cation) is useful for modelling ionophore-cation interactions in biological membranes and the investigation of the lipid-peptide interaction at the interfaces. The surface pressure - and surface potential - molecular area isotherms for mixed monolayers of valinomycin and lipids at aqueous salt subphases were measured. Two additional states of valinomycin-lipid monolayers as particular complex types were observed in the presence of K^+ as compared with Na^+ in the aqueous subphase.
Monolayers of the crown-ether derivatives (CED) modified with long hydrocarbon chains can serve as unique models for the investigation of molecular recognition and interaction phenomena at interfaces, as well as potential nanomaterials for many applications. In particular, the amphiphilic photosensitive benzodithia-15(18)-crown-5(6) ethers formed stable insoluble monolayers on distilled water and aqueous solutions containing heavy metal cations (collapse pressures 33 and 31 mN/m for Ag^+ and Hg^{2+} salts). It was shown by measurements of the surface pressure – and surface potential – area per CED molecule isotherms that heavy metal cations formed complexes with CED in monolayer. These conclusions confirmed by Brewster angle microscopy and by reflection intensity measurements on water and various aqueous salt subphases. The kinetics of the spectral reflection intensity changes under irradiation of the CED monolayer on aqueous and different salt subphases gives an additional information about crown–cation interactions. The use of special polymer matrixes leads to the reversible changes of the spectral reflection intensity of mixed CED monolayers in the presence of heavy metal cations. This approach is promising for construction of nanomaterials with desirable chemosensoring properties.
This work was supported by grants of the RFBR (10-03-00711) and the Russian Ministry of Education and Sciences (02.740.11.0718).

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MONOLAYERS BASED ON BACTERIORHODOPSIN AS PROMISIMG NANO-BIOMATERIALS

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Design, investigation, and applications of membrane-like systems based on bacteriorhodopsin (bR), a photosensitive membrane protein, is a rapidly growing field at the interface of materials and life sciences. Purple membranes

(PMs), which are fragments of membranes of the bacteria *Halobacterium halobium* or *H. salinarum* where bR is the main protein component, are the most typical and well-described examples of such membrane-like systems. It is known that bR transforms physical energy (light quanta) into chemical energy of macroergic compounds (e.g., ATP) or mechanical energy (e.g., flagellar movement in bacteria). It should be emphasized that bR and PMs possess unique physicochemical properties and fulfil three main molecular functions that are crucial in terms of fundamental studies and technological applications: photoelectric, photochromic, and proton-transporting.
The fabrication of ultrathin, highly oriented bR films is one of the key tasks for prospective applications of bioinspired hybrid materials and devices. One of the most promising methods is preparation of bR monolayers at the liquid/air or solid/air interfaces by the Langmuir–Blodgett (Langmuir–Schaefer) method.
The area per bR molecule in the monolayer (upon extrapolation to a zero pressure) on the surface of a 100-mM KCl solution has been estimated to be 8 nm^2, which agrees with the X-ray data on the protein structure in the membrane obtained by Henderson et al. using an elementary cell 2.5 x 3.5 x 4.5 nm in size. A steep rise of the isotherm of the surface pressure versus area per protein molecule and a high monolayer collapse pressure (higher than 45 mN/m) indicate the formation of sufficiently strong bR monolayers on concentrated salt subphases. In addition, these structures have been found to have a high photopotential when illuminated through a filter with a bandpass of 570 ± 15 nm.
These ultrathin, highly oriented bR films may be regarded as promising nano-biomaterials for photovoltaics, biosensing, and development of optical and optoelectronic devices.

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THE NOVEL DIAGNOSTIC METHOD FOR THE EARLY DRUG ADDICTION REVEAL

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METAL NANOPARTICLES STABIZED BY POLYVINYLPIRROLIDONE

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Argentums nanoparticles were obtained by reflux method in polyvinylpyrrolidone solutions. Influence of such synthesis conditions as salt and solvent nature, molecular weight of polymer stabilizator was studied. It was shown that the reduction process goes faster and easier for argentums acetate than for argentums nitrate and also in aprotonic solvents (dimethylformamide, dimethylsufoxide) than in ethanol. This data were used for synthesis of copper, cobalt and nickel nanoparticles. Nanoparticles of these metals with average sizes about 2-3 nm were obtained from their acetates in presence of polyvinylpyrrolidone in dimethylformamide and dimethylsulfoxide without usually used strong reducers as hydrazine, sodium borhydride and others.

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CLICK CHEMISTRY AS A POWERFUL TOOL FOR CONJUGATION OF TARGETING PEPTIDES TO POLYMER CARRIERS

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The application of azide-alkyne cycloadditions – "click" chemistry for conjugation of two molecules of defined structure is described in increasing number of publications. Due to high selectivity the "click" chemistry is often used in the synthesis of polymer drug conjugates, e.g. conjugates with targeting peptides.
In our work, we prepared biologically active peptides bearing the *N*-terminal azide group using solid phase strategy and we needed to "click" these targeting peptides to polymer carriers of an anticancer drug doxorubicin bearing the triple bonds along the polymer chain. Unfortunately, the most commonly used "click" chemistry reaction catalyzed by copper (I) in both aqueous and organic solvents leads to insoluble products because doxorubicin forms a complex with Cu (I).
For this reason, we used for the "click" reaction with polymer conjugate catalysis based on ruthenium complexes. However, use of ruthenium complexes was primarily limited by their solubility and moreover, the oxygen sensitivity of the catalyst persisted thus limiting applicability of this catalyst for peptide conjugation.

Therefore, we have studied the coupling of azide-peptide to the polymers bearing derivatives of dibenzocyclooctyne (DBCO) - the so-called metal-free click chemistry. This conjugation reaction was carried out both in organic solvents and in aqueous solutions and did not require inert atmosphere.
After selection of a suitable conjugation system we focused on the preparation of semitelechelic polymers bearing DBCO group at one end of the polymer chain using controlled radical polymerization – reversible addition-fragmentation chain transfer (RAFT) polymerization providing polymers with very narrow distribution. Our initial attempts to synthesize the polymers using azo-initiator and chain transfer agent both containing DBCO groups did not lead to polymers with desired size and functionality. However, post-polymerization substitution of the terminal dithiobenzoate group of the polymer (originating from the chain transfer agent) with an azo-DBCO derivative yielded a semitelechelic DBCO-terminated polymers.
In conclusion, we have demonstrated the possibility of using "click" chemistry for conjugation of the unprotected azide-peptides to DBCO-terminated polymers resulting in conjugates with low polydispersity. The alkyne-azide cycloaddition proved to be a very efficient and chemoselective method of binding of unprotected peptides to polymer carriers of drugs.

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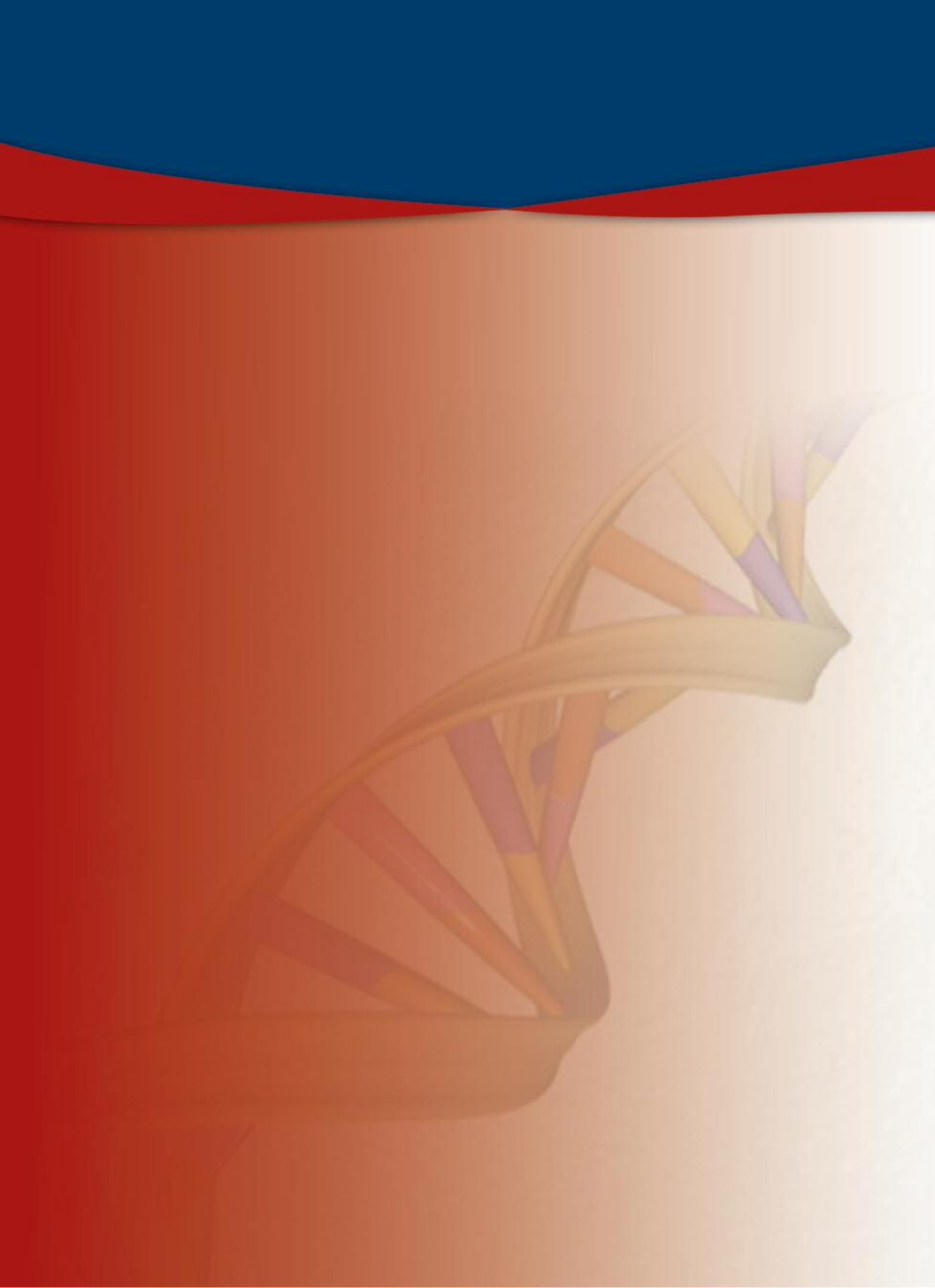
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