УДК 612:539.12+617.7+57.086.15 Надійшла 12.12.2010

I. S. CHEKMAN, Z. R. ULBERG, N. O. GORCHAKOVA, T. YU. NEBESNA, T. G. GRUZINA, A. O. PRISKOKA, A. M. DOROSHENKO, P. V. SIMONOV (Kyiv, Ukraine)

THE PROSPECTS OF MEDICAL APPLICATION OF METAL-BASED NANOPARTICLES AND NANOMATERIALS

National O.O. Bogomoletz Medical University, The F. D. Ovcharenko Institute of Biocolloidal Chemistry of National Academy of Sciences of Ukraine

Current studies, dedicated to metallic (gold, silver, iron, and copper) nanomaterials are reviewed in this paper. This metals own unique physical and chemical properties which determine their application. The medical application of metallic nanomaterials includes therapy and prophylaxis of diseases, development of new drugs and improvement of conventional ones, nanodiagnostics. Nevertheless some aspects concerning the introduction of the nanometals into medical practice need further profound research.

Key words: nanotechnology, nanomedicine, nanopharmacology, metallic nanoparticles, nanomaterials.

Introduction. The evolving of nanotechnology generated different nanoscale-sized materials and metal-based ones are one of the most interesting and promising among them. Nowadays thousands of articles in various specialized journals all-over the world are published and dedicated to different metallic nanomaterials. The unique physical (e. g. plasmonic resonance, fluorescent enhancement) and chemical (e. g. catalytic activity enhancement) properties of nanometals are as a result of high quantity of surface situated atoms and high area/volume relation. Metal nanoparticles found their application in engineering, chemistry, biology, medicine. The medical applications of metal nanomaterials (nanoparticles, nanocomposites, nanocoatings) may be divided as follows:

- therapy (e. g. photothermal cancer treatment using nanogold [72], or using cytotoxic effect of iron-based nanomaterials [56]);
- specific detection of biomolecules and drugs, nanodiagnostics [52, 77];
- prophylaxis (e. g. antimicrobial silver nanocoating on catheters for prevention of infections [144]);
- creating new drugs and medicinal products or improvement of conventional ones [21, 76, 129].

Nevertheless, some fields of using nanometals (controllable commercial synthesis, toxicological properties, safety for environment, and ethical issues) are still requiring further profound research. The aim of this review article is to focus on the most studied metal nanoparticles (gold, silver, iron, copper), their potential use in medicine.

Nanogold. In biomedical researches most often used types of gold nanoparticles (AuNPs) are nanorods, nanospheres and nanoshells [31, 72, 142]. Nanotubes, nanoparticles with irregular form and nanocoatings are used less frequently.

Intensive researches in nanomedicine have formed a distinguished direction – **nanodiagnostics**. Nanodiagnostics – is an application of nanotechnology and nanomaterials in clinical diagnostics [77]. According to the classification of [16] diagnostics, based on gold nanoparticles, may be divided into three approaches:

1. *Utilization of the AuNPs color change upon aggregation.* The best characterized example being AuNPs functionalized with ssDNA capable of specifically hybridizing

to a complementary target for the detection of specific nucleic acid sequences in biological samples [141].

2. *Use of AuNPs as a core/seed that can be tailored with a wide variety of surface functionalities to provide highly selective nanoprobes for diagnosis (e. g. electrochemical immunosensors)*. An integrated automatic electrochemical immunosensor array has been designed for the simultaneous detection of type-5 hepatitis virus antigens (i. e. hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E) [148]. Initially, type-5 hepatitis virus antibodies were immobilized onto a self-made electrochemical sensor array using nanogold particles and protein A as matrices. The detection is based on the potential change before and after the antigen-antibody interaction by using a 2-electrode system. The developed immunosensor array allows simultaneous determination of type-5 hepatitis virus antigens in 5 min. The detection limit of the sensor array was < or = 1 ng/mL. Based on gold label silver stain and coupled with multiplex asymmetric polymerase chain reaction analysis, the visual DNA microarray for simultaneous, sensitive, and specific detection of human immunodeficiency virus type-1 and Treponema pallidum was developed [149].

An electrochemical impedimetric immunosensor was developed for ultrasensitive determination of insulin-like growth factor-1 based on immobilization of a specific monoclonal antibody on AuNPs modified gold electrode [131]. Nanogold in size of 10 nm was used to label goat anti-human IgG to obtain an immunonanogold probe for IgG [150].

3. *Use of AuNPs in electrochemical methods, associated with metal deposition for signal amplification*. A sandwich-type electrochemical immunosensor with enhanced sensitivity was designed for detection of alpha-fetoprotein (marker of hepatocarcinoma) in biological fluids by using nanogold-enclosed titania nanoparticle-labeled secondary antibody on a gold-silver-graphene (AuAgGP) hybrid nanosheet-functionalized glassy carbon electrode [145]. The presence of the AuAgGP nanosheets enhanced the immobilized amount of biomolecules and improved the electrochemical properties of the immunosensor.

AuNPs are also used in **pharmacotherapy of diseases**. Photothermal therapy – is a method of treatment, grounded on a phenomenon of surface plasmon resonance. AuNPs absorb near-infrared light and convert its energy into local heat. This process is accompanied by destruction and bubbles formation [121]. AuNPs linked to antibodies can selectively destroy the target-cells under influence of Ti:Sapphire laser. Gold nanoparticles conjugated to anti-epidermal growth factor receptor monoclonal antibodies specifically and homogeneously bind to the surface of cancer cells with 600 % greater affinity than to noncancerous cells [78]. Intravenous administration of AuNPs enhanced radiation therapy when treating the radiation resistant and highly aggressive mouse head and neck squamous cell carcinoma model [66]. AuNPs thus offer a novel class of selective photothermal agents using mostly for treatment of superficial tumors (e. g. squamous-cell carcinoma) [50, 71]. Another important area of photothermal therapy application – is treatment of infections caused by multiresistant strains of microorganisms. For example, gold nanorods that have been covalently linked to primary antibodies destroyed the pathogenic Gram-negative bacterium, Pseudomonas aeruginosa [121].

Nanogold is used in **drugs detection** in biological objects. E. E. Ferapontova et al. [52] designed a biosensor for detection of the bronchodilator theophylline in serum. The 5'-disulfide-functionalized end of the RNA aptamer sequence was immobilized on a gold electrode, and the 3'-amino-functionalized end was conjugated with a ferrocene redox probe. Upon binding of theophylline the aptamer switches conformation from an open unfolded state to a closed hairpin-type, resulting in the increased electron-transfer efficiency. Theophylline is detected with high selectivity in the presence of caffeine and theobromine. S. Y. Hou et al. [68] developed a dot-blot gold nanoparticle immunoassay to detect target molecules, such as dioxin, digoxin and mercury salts.

Gold nanoparticles are used in **cytological and cytogenetic studies** to get clear images of cell structures and investigate their functions. In research of K. Oyelere et

al. [123] gold nanorods covalently conjugated with a nuclear localization signal peptide were incubated with an immortalized benign epithelial cell line and an oral cancer cell line. Dark field light surface plasmon resonance scattering images demonstrated that nanorods are located in both the cytoplasm and nucleus of both cell lines. The Raman spectra reveals the difference between benign and cancer cell lines. The work represents an important step toward both imaging and Raman-based intracellular biosensing.

G. Guigas et al. [62] have used uorescence correlation spectroscopy to determine the anomalous diffusion properties of uorescently tagged gold beads in the cytoplasm and the nucleus of living cells in normal and osmotic stress conditions. Another important research [91] was devoted to the imaging of pH in live cells by mobile and biocompatible nanosensors using surface-enhanced Raman scattering of 4-mercaptobenzoic acid on gold nanoaggregates. Designed sensor enables measurements over a wide pH range without the use of multiple probes. I. U. Vakarelski et al. [155] have fabricated robust nanosurgical needles suitable for single cell operations by modifying multiwalled carbon nanotube-terminated atomic force microscopy tips with an outer shell of gold. The terminal diameters of the final fabricated tips were approximately 30–40 nm, such tips can easily penetrate the plasma membrane of living cells at the smallest indentation depths (100–200 nm) and lowest penetration forces (100–200 pN) currently reported for these procedures. An outer layer of gold enhanced their versatility and ease of conjugation with a variety of chemicals, nanoparticles, drugs and biological molecules.

A new method of optical microscopy – antenna-based near-field optical microscopy – was developed by C. Hoppener et al. [67]. An optical antenna in the form of a single gold nanoparticle to localize incident laser radiation to 50 nm (significantly smaller than the diffraction limit of light) was used. This approach enables researchers to optically resolve individual plasma-membrane-bound Ca^{2+} pumps immersed in aqueous environments and to determine the distribution of interprotein distances. Antenna-based near-field optical microscopy will make it possible to resolve, identify, and probe single membrane proteins in live cells with true protein resolution of 5–10 nm. Molecular study of Ca^{2+} pumps is important for treatment of such diseases as arterial hypertension, heart disorders, diabetes, Alzheimer's disease, sickle cell anemia, muscular dystrophy, cystic fibrosis, chronic kidney diseases.

M. Hu et al. [70] developed a labeling method to prepare protein 2D arrays using AuNPs interconnecting genetic tag sites on proteins. As an example, mycobacterium tuberculosis 20S proteasomes tagged with 6x-histidine were assembled into 2D arrays using 3,9 nm AuNPs functionalized with nickel-nitrilotriacetic acid.

AuNPs are used in drug and gene delivery. Lamin A/C, an important nuclear envelope protein, was effectively silenced by lamin A/C-siRNA delivered by charge-reversal functional gold nanoparticles, whose knockdown efficiency was better than that of commercial Lipofectamine 2000 [63]. Liposomes labeled with nanogold were used to target atheromas in a Watanabe heritable hyperlipidemic (WHHL) rabbit model. Liposomes were concentrated in areas of lipoprotein-associated phospholipase A_2 expression. Modified liposomes can be delivered to the shoulder regions of advanced atheromas in WHHL rabbits and may be useful therapeutically for targeting metabolically active plaque [156].

Although gold compounds have been used as a potential drug for the treatment of rheumatoid arthritis, some adverse effects, such as skin irritation, dermatitis, stomatitis, contact allergy, and hypersensitivity reactions were associated with over exposure to gold compounds [127]. According to Y. Pan et al. [125] the cytotoxicity of AuNPs was checked by including them with various incubating cell lines; for example, cervix carcinoma epithelial cells (HeLa), SK-Mel-28 melanoma cells (SK-Mel-28), L929 mouse fibroblasts (L929) and mouse monocytic/macrophage cells. There are two types of cell death in the cell lines: a rapid cell necrosis (caused by membrane damage; the products released by this necrotic process are also highly inflammatory) and apoptosis (doesn't involve membrane damage and inflammation). W. S. Cho et al. [33] studied the *in vivo* toxic effects of 13 nm size polyethylenglycol- (PEG) coated AuNPs

on mice. The nanoparticles were seen to induce acute inflammation and apoptosis in the liver. They accumulated in the liver and spleen for up to 7 days after injection and had prolonged blood circulation times. Because PEG-coated AuNPs are widely used in biomedical applications these effects have obvious clinical implications.

However with the increasing interest in studying gold nanoparticles, one should pay attention to their biosafety and peculiarities of interaction with living cells. Z. R. Ulberg group [1–5, 41–44, 85, 153, 154] have shown mechanisms of some bacteria cells interaction with spherical gold nanoparticles of average size 20 nm. The cells used in the experiments were representative heterotrophic bacteria, such as *Bacillus cereus*, *Bacillus fascidiosus*, *Bacillus subtilis*, and *Pseudomonas iodinum*, and microalgae such as *Chlorella vulgaris*. Intriguingly, the interaction occurred in two stages: the nanoparticles were initially bound to the cell very weakly and reversibly but in the second stage, the reversible aggregation gradually became irreversible over 1h. The first stage, reversible aggregation, was the most peculiar. It was very sensitive to specific metabolism inhibitors and, consequently, was under the control of the cell's energetic metabolism. Fig. 1 demonstrates results with pentachlorophenol.

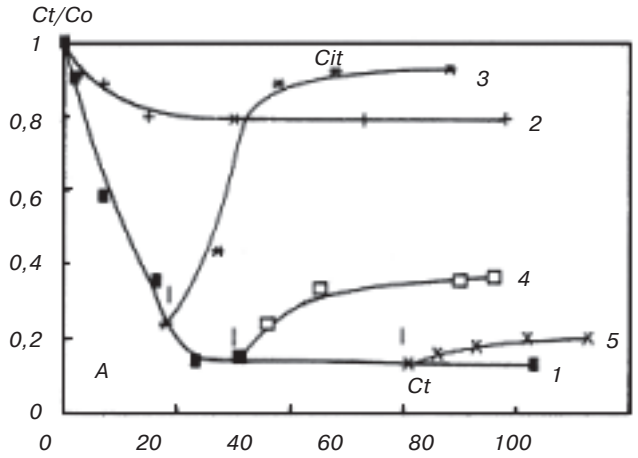
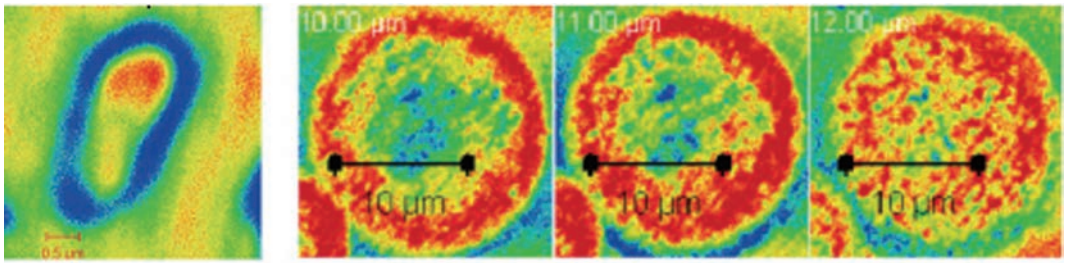


Fig. 1. Kinetic curves of the gold nanoparticles adsorption by bacteria Bacillus cereus B-4368, where C_t is a relative concentration of gold nanoparticles in the solution. Curve *1* is uninterrupted adsorption. Curve *2* is adsorption when pentachlorophenol is initially added to the solution. Curves *3*, *4* and *5* represent the kinetics after injection of pentachlorophenol at different time points [44]

Injection of pentachlorophenol released gold nanoparticles back into the solution. The amount of released particles decreased with increasing incubation time of the nanoparticles with the cells, suggesting that the aggregation went from reversible to irreversible. Several other inhibitors were used that shared a common feature – they dissipate the proton-motive force or disturb the work of ion pumps that generate this force. The inhibitors were sodium azide and rotenone for blocking the respiratory chain, dicyclohexylcarbodiimide (DCCD) that inhibited proton ATPase, and arsenate that damaged synthesis of ATP. The reversible aggregation was specific for live cells only. Dead cells aggregating with gold nanoparticles did not exhibit this feature. Inactivation of the bacterial cells by thermal shock resulted in losing the capability to accumulate colloidal gold. Most convincing was influence of light on the interaction of algae cells with colloidal gold: cells of green microalgae, *Chlorella vulgaris*, sufficiently decreased the amount of accumulated gold after putting the cell suspension in a dark box [44, 85, 152]. These data shows that interaction of live cells with AuNPs depended on the membrane-energy transformation processes.

During this experimental work the peculiarities of size-dependent interaction of synthesized spherical gold nanoparticles (average sizes 10, 20, 30 and 45 nm) with bacteria (probiont strains) and eukaryotic (CHO-K1 and U937 cell lines) cells have

been determined [73, 132]. Confocal-microscopic images of *E. coli* bacteria cells and U937 eukaryotic cell with accumulated gold nanoparticles are presented on fig. 2.



a *b*

Fig. 2. Confocal-microscopic image of *E. coli* bacteria cells (*a*) and U937 eukaryotic cell (*b*) with accumulated gold nanoparticles

Stimulation on 20–40 % the H^+-ATP-ase activity of bacteria cells' membrane fraction, on 30–50 % – β-lactamase activity of *E. coli* bacteria and stabilization in concentration 1,1 mcg/ml by metal of the gramnegative (*E. coli*) as well as grampositive (*Ent. faecalis*) bacteria cell walls by gold nanoparticles with average size 30 nm has been established [7, 132, 133].

The concentration optimum (0,1–1 ng metal per cell) and fast kinetics (3–5 min) of the process of AuNPs contact interaction with eukaryotic tumor U937 cells have been determined in the *in vitro* experiments. AuNPs size-dependent influence on Na^+,K^+-ATP-ase and lactate dehydrogenase activities of U937 tumor cells have been shown [133, 134].

In works [43, 44] with using of genotoxicity as biomarker of nanomaterials' risk assessment the 30 and 45 nm AuNPs biosafety under the conditions of interaction with CHO-K1 as well as U937 cells has been established. In contrast, the 10 and 20 nm AuNPs possess genotoxic influence for both types of the cells.

Thus, AuNPs are used in molecular diagnostics, therapy, drugs detection, cytologic studies. It should be specially noted that AuNPs offer new possibilities in the therapy of cancer and infectious diseases. However, there are certain difficulties in implementing them in practical activities related to the problem of reproducibility, biological and toxicological aspects [15, 151]. Nevertheless, in future it is hoped that these issues will be resolved, because AuNPs have opened new possibilities in medicine, unattainable by traditional methods.

Nanosilver. Silver has been known for its antimicrobial properties since ancient times [4]. However, the first medical preparations with this metal were made only in the XIX-th century. Silver nitrate was quite effective agent against different microorganisms but in the 40s of the XX-th century interest to silver preparations had decreased greatly, when antibiotics were discovered [45]. Later, with the rise of nanotechnology this interest increased again, when it became possible to manufacture different materials with defined shape and size at the nanoscale level. Nowadays nanostructured silver is studied very extensively especially for medical purposes.

Pharmacological properties of nanosilver

In contrary to conventional silver preparations, nanostructured ones have improved pharmacokinetics [20, 45]. Nanosilver has significant anti-inflammatory effect that was shown by K. C. Bhol et al. [21] and J. Jain et al. [76], immunomodulative [21] and antiviral [17, 48, 97, 98, 108, 143] effects. But the most prominent and well-studied is antimicrobial effect of nanosilver. It is known that silver nanoparticles and nanocoatings could be an effective agent against not only gram-negative and positive bacteria but also fungi in concentration of about tens milligrams per liter [92, 137]. Furthermore, some researchers report about synergistic effect of silver nanoparticles and antibiotics [51, 76]. Nevertheless the mechanism of antimicrobial effect has not been completely clarified yet. The possible mechanism of silver nanoparticles action on the

microbial cell was described in works of Q. Li et al. [103] and D. M. Aruguete et al. [11]. Nanoparticles accumulate at the surface of the cell wall, degrade lipopolysaccharides and form "pits" of high permeability. Then nanoparticles penetrate cell wall through this pits, release silver cations in cytoplasm, cause the forming of reactive oxygen species, and bind to cytochromes thus blocking respiratory chain. Some authors allow that silver ions can interact with DNA and block its replication [45]. It is suggested that antimicrobial properties of silver nanoparticles are dependent on their geometrical parameters. Thus O. Choi et al. [35] showed that inhibition of nitrifying bacteria is correlated with fraction of 5 nm-sized silver nanoparticles. S. Pal et al. [124] performed a study which elucidates dependence of antimicrobial activity of silver nanoparticles from their geometry. They determined that triangle-shaped nanoparticles are more effective than spherical and rod-shaped types against *E. coli*. Despite the fact that silver has broad spectrum of antimicrobial activity and resistance to this metal is formed very rarely, there are already mentioned some mechanisms of resistance formation in *Salmonella typhimurium*, *E. coli* strains [36] and *Bacillus cereus* [102]. Researchers also note that resistance may be as a result of using nanosilver in concentrations below minimal inhibition concentration (MIC) [42]. Another effects of nanosilver are anti-inflammatory and immunomodulative which are associated with suppression of cytokines synthesis, and inhibition of matrix metalloproteinases [21, 45].

Nanosilver as a potential treatment agent

With increasing interest to nanostructured silver a number of medical preparations and products were made with adding of this metal. These are predominantly topical medicines such as crèmes [21], gels [76] and dressings [20, 45]. Some of them passed clinical trials and available for patients' treatment [45]. Preparations with nanosilver are effective in treatment of wounds and burns, allergic contact dermatitis and skin microbial infections. Silver nanoparticles could be combined with natural or synthetic polymers to improve their efficiency and obtain new effects. For example, chitosan-silver composites have not only antibacterial activity but also decrease blood clotting time [111]. Another study has been dedicated to the so-called polyrhodamine-silver nanofibers, which have significant antimicrobial effect which was greater than conventional silver-sulfadiazine preparation [92].

Other medical applications of nanosilver

Silver nanocoatings could be effective in preventing hospital infections when deposited on intravenous catheters [144]. The ability of silver nanoparticles to increase greatly fluorescence emission formed the basis of so-called "silver enhancement" technique which is useful for diagnostic purposes [29]. Silver nanoparticles as well as gold own specific optical properties, and can be useful in surface enhanced Raman spectroscopy [83], sensing and imaging [101].

Toxicological aspects of using silver nanoparticles

Despite nanostructured silver being one of the most extensively studied nanomaterials, the toxicological aspects of its use still remain a question. It is necessary to provide *in vitro* studies of cytotoxicity, genotoxocity, and mutagenic action of nanoparticles, and *in vivo* studies, as well due to a lack of data about acute and chronic toxixcity of nanosilver. It is known that silver nanoparticles may be cytotoxic to both differentiated and non-differentiated cell lines [10, 115, 138]. Genotoxic action on cells is important point in assessing of nanomaterials safety. Nowadays it is determined that silver nanoparticles with different shape, size and stabilizers could be genotoxic to prokaryotic [59] and eukaryotic cells [6, 39, 95, 119, 126, 160], including human cell lines [12, 54]. However, the cytotoxic concentrations were higher than therapeutic. Most researchers associate cytotoxic and genotoxic effects with formation of reactive oxygen species (ROS) under the influence of Ag^+-ions, promoting of DNA-damage and generation of oxidative stress [89]. Studies provided on different aquatic invertebrates and pisces also show that silver can be toxic to this organisms and impair their reproductive system [23, 61, 96, 160, 165].

The acute toxicity data concerning silver nanoparticles is poor and quite contradictory. The LD_{50} of nanocrystalline silver (spherical nanoparticles 7–20 nm in diam-

eter) in form of gel for topical use was assessed about more than 2000 mg/kg for Sprague-Dawley rats (skin application), and researchers made a conclusion that this nanomaterial could be considered as safe for topical use [76]. In the study of G. Ordzhonikidze et al. [122] the LD_{50} for intraperitonial injection of stabilized silver nanoparticles (size 9nm ± 6 nm) for BALB/c mice was $1{,}9 \cdot 10^{-6}$ mg/gm of animal weight. The changes in organs and systems function after repeated administration of silver nanoparticles (sub-chronic and chronic toxicity) are also uncleared. In the studies of J. H. Ji et al. [79, 90, 147] 28-day experiments were established with two routes of administration (inhalation and oral) on Sprague-Dawley rats. They determined in what organs nanoparticles could accumulate and how did biochemical parameters changed during experiment. Researchers also marked that accumulation of silver nanoparticles in rat female kidneys is more than two-fold higher than in male ones.

According to mentioned above we can make a conclusion that nanomaterials made of silver or with adding this metal are very prospective in context of their medical applications. Their potential use includes:

– development of new medical preparations and improvement of conventional ones;
– imaging and nanodiagnostics;
– prophylaxis of hospital infections.

Due to pharmacological properties of silver nanoparticles (antimicrobial, anti-inflammatory, immunomodulative) there is a necessity in further research concerned with toxicological aspects and safety for human use and environment.

Iron-based nanomaterials. The more bulk iron is dispersed, the more evident become its physical and chemical properties. As a result one can observe enhancement of chemical reactivity and magnetic features of micro-sized iron particles that made them useful in chemical industry as catalysts, in electronics as magnetic data carriers. Further miniaturization in the nanoscale direction that has taken place during the last two decades has led to thorough studying of nanoiron. Term “nanoiron” has an integrative meaning and involves nanosize iron-based materials such as zero-valent iron (ZVI) nanoparticles, iron oxide nanoparticles also known as superparamagnetic iron-oxide nanoparticles (SPIONs), and iron-based nanocomposites. The main advantages of nanoiron among other nanomaterials are relatively low toxicity and biodegradation. In addition, iron is relatively cheap and widespread material [74].

Zero-valent iron nanoparticles

Iron typically exists in the environment in an oxidized state, and as such, ZVI is a manufactured material. The use of ZVI as a remediation agent in groundwater and soil treatment started in 1990s when granular ZVI was first employed in permeable reactive barrier systems. Recent research in the utilization of ZVI nanoparticles for treatment of contaminated soils and groundwater can be regarded as an extension of the ZVI technology [106].

ZVI nanoparticles typically exhibit core-shell morphology. Due to oxidation of surface atoms metallic core is coated with iron oxide (maghemite and magnetite) or hydroxide shell. While ZVI acts as electron donor during chemical reactions, oxide/hydroxide shell is involved in chemical complexes formation (chemosorption) [114]. In addition, corrosion of iron in the presence of oxygen leads to formation of hydroxyl radicals and other oxidants [80]. According to these processes ZVI nanoparticles cause degradation of various organic contaminants, such as chlorinated organic solvents, organochloride pesticides (lindane, DDT), polychlorinated biphenyls, organic dyes. ZVI nanoparticles can rapidly remove and/or reduce inorganic ions, such as metal ions Cd, Ni, Zn, As, Cr, Ag, Hg, U, and Pb, as well as notorious inorganic anions like perchlorate and nitrate, and also have relatively higher capacity than conventional sorptive media and granular iron particles [32, 49, 105, 162].

Several groups revealed that ZVI nanoparticles exhibit antimicrobial properties against Gram-negative *E. coli, Pseudomonas fluorescens* and Gram-positive *Bacillus subtilis var. niger* microorganisms [40, 88, 100]. C. Lee et al. [100] reported that inactivation of *E. coli* by ZVI nanoparticles could be because of the penetration of the small

particles (size ranging fron 10–80 nm) into *E. coli* membranes. ZVI nanoparticles could then react with intracellular oxygen, leading to oxidative stress and causing disruption of the cell membrane. In addition, iron oxide nanoparticles also possess antimicrobial properties. N. Tran et al. [152] showed that at the highest tested dose of polyvinylalcohol- (PVA) coated iron oxide nanoparticles (3 mg/mL), the growth of Gram-positive *Staphylococcus aureus* was inhibited significantly compared with the control samples.

Superparamagnetic iron oxide nanoparticles (SPIONs)

In great number of biomedical applications nanoparticles of iron oxide are widely exploited due to their chemical stability and low toxicity. SPIONs with appropriate surface chemistry can be used for numerous *in vivo* applications, such as MRI contrast enhancement, hyperthermia, drug delivery, tissue repair, immunoassay, detoxification of biological fluids, and cell separation. In addition SPIONs are used for treatment of iron deficiency anaemia (IDA). The term superparamagnetic refers to the characteristic strong paramagnetic nature of the particles at nanoscale. SPIONs have much larger magnetic susceptibilities (compared with strictly paramagnetic materials) as the entire crystal aligns with the applied field due to its single crystal nature. Hence SPIONs are useful as contrast agents or for hyperthermic treatment of malignant tumours [81].

SPIONs typically consist of two components, an iron oxide core of one or more magnetic crystallites embedded in a coating. The SPIONs' core can be composed of magnetite (Fe_3O_4) and/or maghemite (γ-Fe_2O_3). Maghemite is the ferrimagnetic cubic form of iron (III) oxide and it differs from the inverse spinel structure of magnetite through vacancies on the cation sublattice [37, 159].

Pharmacological properties of SPIONs are strongly dictated by their physicochemical properties, such as size, charge, hydrophilicity/hydrophobicity, and surface chemistry. Different monomeric (carboxylates, phosphates), inorganic (silica, gold, gadolinium), and polymeric (dextran, polivinil alcohol, chitosan, PEG etc.) surface coatings are used to improve nanoparticles' solubility, stability, reduce toxicity, immunogenicity and phagocytosis. The stability of a magnetic colloidal suspension results from the equilibrium between two attractive (van der Waals and magnetic dipolar) and two repulsive (electrostatic and steric) forces [99].

Size of SPIONs makes important contribution to their fate in organism. Categories of SPIONs, based on their overall diameter (including iron oxide core and hydrated coating), are noted in the literature as oral or micron-sized SPIONs between 300 nm and 3,5 μm; standard or small SPIONs (SSPIONs) at approximately 60–150 nm; ultrasmall SPIONs (USPIONs) of approximately 10–50 nm; and monocrystalline iron oxide nanoparticles (MION – a subset of USPIONs) of approximately 10–30 nm. MION are so named to underline the single crystal nature of their core. This is in contrast to SPIONs greater than 50 nm that are comprised of multiple iron oxide crystals [117].

Oral SPIONs, such as ferumoxsil (GastroMARK®, AMAG Pharmaceuticals) or ferristene (Abdoscan®, GE Healthcare), are used for contrast enhancement of gastrointestinal tract on MRI [65]. A sufficiently long blood half-time of USPIONs, such as ferumoxtran-10 (Combidex®, AMAG Pharmaceuticals), is in most cases favorable for delivering the magnetic nanoparticles in deep territories and then actively targeting the pathological tissues. These nanoparticles may improve visualization of metastatic lesions in reticuloendotelial system (RES) or be useful during MR-angiography [104].

SPIONs may be administered orally or intravenously. Iron from orally administered SPIONs may replenish iron pool in organism. The clearance of iron oxide nanoparticles intravenously injected is strongly related to the opsonization process, i.e. adsorbtion of opsonins, such as circulating plasma proteins including complement proteins, fibronectin, immunoglobulins, on the surface of nanoparticles. Opsonins are capable of interacting with specialized plasma membrane receptors on macrophages, and promoting the particle recognition by these cells. As a result, spleen, liver, and bone marrow become the most accessible tissues as they are rich in macrophages [75, 116]. Moreover,

SPIONs may accumulate in a focus of inflammation or degeneration associated with high phagocytic activity, such as atherosclerotic plaque, ischemic stroke etc [93, 136]. Nanoparticles larger than 200 nm are sequestered by the spleen via mechanical filtration and then are taken up by the RES [116]. Particles down to 100 nm or below, are poorly recognized by Kupffer cells. H. S. Choi et al. [34] recently demonstrated that particles with hydrodynamic size smaller than 5,5 nm are rapidly removed through renal clearance. Larger particles undergo biodegradation in RES and the metabolized iron is incorporated into hemoglobin [28, 158].

Taking into account the pharmacokinetics of nanoparticles it is possible to create nanoiron-based antianemic drugs. Ferumoxytol (Feraheme™, AMAG Pharmaceuticals) is an intravenous iron preparation for treatment of the anemia of chronic kidney disease. It is a carbohydrate-coated USPION that is undergoing clinical trials [139].

Composite inorganic iron-based nanomaterials

Attempts to create multifunctional nanomaterials or nanomaterials with improved magnetic properties than that of SPIONs led to the synthesis of composite inorganic iron-based nanomaterials. A. Figuerola et al. [53] categorized all these nanostructures based on their levels of compositional and/or structural complexity: 1) nanostructures made of an iron-based magnetic material different from iron oxide; 2) nanostructures whose morphology is not a sphere (e. g. hollow structure); 3) multi-material nanostructures, i. e. each of them is made of two or more domains of different inorganic materials joined together.

These approaches can be illustrated by the results of several recent researches. $MnFe_2O_4$ nanoparticles have surpassed SPIONs as contrast agents for MRI *in vivo*. The enhanced sensitivity of $MnFe_2O_4$ nanoparticles was proved *in vivo*, as the $MnFe_2O_4$ nanoparticle enabled detection of a tumor mass as small as 50 mg [9]. Terbium-doped Fe_3O_4 nanoparticles exhibiting at the same time magnetism and fluorescence, and the nanoperticles were non-toxic in the cytological studies [164]. S. T. Selvan et al. [140] reported a synthesis of Fe_2O_3-CdSe dumbbells by direct growth of a fluorescent CdSe domain on the surface of a preformed γ-Fe_2O_3 nanocrystal, after which the dumbbell was encapsulated in a silica shell. The final nanostructure was strongly fluorescent and magnetically active.

In addition to diagnostic applications, composite iron-based nanocrystals can be used for treatment of malignant tumours. Thus, FePt nanoparticles functionalized with luteinizing hormone-releasing hormone (LHRH) peptide have enhanced cytotoxicity against ovarian cancer cells that express LHRH-receptors. In the acidic environment of lysosomes, these nanoparticles release toxic iron species, which catalyze the formation of reactive oxygen. The latter is toxic for cells as it can damage lipid membranes, DNAs, and proteins [161]. Nanoshells CoS_2@FePt also possess better antitumor activity than that of cisplatin [58]. MR-visualisation of a tumour with its destruction prompted scientists to develop nanoshells Fe_3O_4@FePt [56].

Nanoiron–cells interaction strongly depends on physicochemical properties of the nanoparticles. T. Phenrat et al. [128] revealed on rodent brain cells that fresh ZVI nanoparticles was more toxic relative to its "aged" (partially oxidized during 11 months), oxidized (such as magnetite), and surface-modified counterparts. Partial or complete oxidation of ZVI nanoparticles reduce its "redox" activity and cytotoxicity. Surface coating also reduces toxicity of nanoparticles by limiting particles exposure to the cells. Comprehensive study of SPIONs (Ferumoxtran-10) and macrophages interaction *in vitro* showed, nanoparticles was not toxic to cells, did not activate them to produce pro-inflamatory cytokines (interleukin-12, interleukin-6, tumor necrosis factor-α or interleukin-1β) or superoxide anions, was not chemotactic and did not interfere with Fc-receptor-mediated phagocytosis [118]. In another study phagocytic function of macrophages decreased after labelling with only 10 μg Fe/mL SPIONs (ferucarbotran) [69].

Iron-based nanomaterials are thoroughly investigated according to their relatively low toxicity integrated with unique properties in order to exploit them in such biomedical applications as remediation of environment, development of a novel diagnostic tools and methods for individualized treatment.

Nanocopper. Among nanometals, copper (Cu) is the promising candidate for a development of new generation preparations. It's interesting that copper is a trace element and a toxic heavy metal to many living cells simultaneously. On the one hand, copper participates in many major metabolic processes [94]. On the other hand, it shows significant bacteriostatic and bactericidal activity, due to cell membrane, nucleic acid and protein damage [24, 55].

The mechanism of the antibacterial action of copper is predominantly based on DNA structure damage. Copper selectively binds to guanine residues in molecule and activates the oxidative stress that results in a break of one or both DNA strands and a base modification with formation of 8-hydroxy-2'-deoxyguanosine and other products [25, 86, 120].

Nowadays it is known that copper shows biocidal activity not only against bacteria, among which are methicillin-resistant Staphylococcus aureus strains [55, 109, 157], but also against bacteriophages [24] and viruses, such as herpes simplex virus, human immunodeficiency virus [26], bronchitis and influenza viruses [27, 60].

Actually, nanomaterials generally readily participate in chemical reactions than larger objects of similar chemical nature. Therefore, nanomaterials show greater biological activity. This fact set scientists thinking about the possibility of copper nanoparticles' use as the antibacterial and biocidal agents.

Development and improvement of synthesis methods is a very important part in creation of nanometals and study of their properties. Among most frequently used, nanocopper synthesis techniques to date are reverse micelles, the reduction of a copper (II) acetate in water and 2-ethoxyethanol using hydrazine, the reduction of a copper chloride using $NaBH_4$ in the nonionic water-in-oil (w/o) microemulsion, the sonochemical synthesis, the radiolysis method, the use of carbon nanotubes as a template, the photochemical synthesis and the laser ablation [64, 84].

The sonoelectrochemical synthesis method, initially proposed by J. Reisse et al. [130] and improved for nanotechnology purposes by A. Haas et al. [64], utilizes current and sonic pulses for nanoparticles generation.

S. Sahoo et al. [135] proposed the new Cu_2O nanostructures synthesis technique at the room temperature without utilization of any templates or additional reagents – the copper nanocrystals electric field self-assembly. Nanostructures are formed by the anodic oxidation of copper in deionized water.

The promising area of a nanocopper employment is the copper/low-density polyethylene nanocomposites (nano-Cu/LDPE) creation for copper-containing intrauterine devices (Cu-IUD) – one of the most effective contraceptive methods nowadays. Within the first few months of Cu-IUD application the typical side effects such as a uterine bleeding and a pain syndrome occur. That's the reason of the contraception method discontinuation [110]. Nano-Cu/LDPE were developed with the aim to eliminate this shortcoming of Cu-IUD. Devices with nanocomposites impede the burst release behavior of copper ions in the first few months of use. Therefore the side effects are minimized while high antifertility effectiveness is preserved [107].

Methods of synthesis of copper nanotubes, nanospheres, nanorods and nanorings are swiftly developing nowadays. These nanoscaled structures find their fields of application in the medicine. In 2003 I. A. Banerjee et al. [14] synthesized copper nanotubes with the biomineralization method using histidine-rich peptide nanotubes as a template. Copper nanotubes are utilized as the part of biosensors that combine properties of a nanoelectric component (electric properties of nanocopper change with a crystal size alteration) and a biochemical sensor (peptide templates conformation vary under the influence of biochemical factors).

Y. Chang et al. [30] synthesized hollow Cu_2O nanospheres that, due to the great free surface area and the ability to insert ligands into the structure of the cavity, can find an application as transport structures for drug-delivery [146].

Recently developed copper nanorings [19] and nanorods [163] have a potential application in the surface enhanced Raman spectroscopy (SERS), that's an effective method of chemical analysis, the aim of which is to determine a composition and a

molecular structure of observable objects. Metal nanorings and nanorods are promising nanostructures that can be used in SERS for the purpose of disease and pathological state diagnostics [13, 87].

The growth of synthetic nanoparticles' influence on the Earth's biosphere due to their increasing global production is projected in the coming years. From the position of this prospect an attention of scientists was drawn to aspects of nanomaterials safety, their impact on the environment and human health. Carrying out of continuous studies on toxicological properties of nanomaterials and taking into account their results in order to most effectively avoid a negative impact of nanoparticles on a human organism and the biosphere are of great importance [18]. Toxicological properties of nanoparticles depend on numerous factors, such as size, shape, surface area, mass, charge, solubility, purity, pharmacokinetic parameters (routes of entering the organism, absorbability, distribution and excretion) [38, 112].

Nanoscale size may promote the toxicity of particles owing to several reasons:

– the free surface area increases and therefore the dissolution speed and reactivity grow;
– particles are able to overcome cellular and intracellular barriers;
– nanomaterials can interact with subcellular structures, particularly with microtubules and DNA;
– as a result of previous three clauses, pathological and physiological responses of the organism may occur, among which are inflammation, fibrosis, allergic reactions, genotoxicity and carcinogenicity [73].

Impact of nanocopper on a human health and the environment is partially known, despite the increase in the rate of introduction of copper nanomaterials in medicine. A research in this direction is being actively conducted today [82, 113].

Despite the broad spectrum of toxic activity of nanomaterials, including copper nanostructures, nanotechnologies keep on developing and improving. Optimization of nanocopper synthesis and stabilization technology, change of its physicochemical properties are the main objectives in reducing toxicity of promising copper nanomaterials.

We can conclude that special attention of scientists is paid to copper nanomaterials. Medications with copper nanoparticles may be considered as promising antibacterial drugs. In addition, applied in IUD, nanocopper shows contraceptive activity with low intensity of side effects. Technology of copper nanoparticle synthesis has to be further improved with the purpose of generating homogeneous monodisperse nanocopper fractions. Toxicological properties of copper nanoparticles and means of safe nanopreparations' development have to be studied more thorough too.

Conclusion. Metallic nanomaterials are widely researched at present, and gold-, silver, iron-, and copper-based are promising in medical field. Nanogold found its application mostly in immunodiagnostics and cancer treatment, nanosilver is prospective antimicrobial, anti-inflammatory and immunomodulative agent, nanoiron could be used in diagnostics and therapy of cancers and in treatment iron-deficiency states, and nanocopper may be useful in construction of biosensors, and as antimicrobial and contraceptive agent. Nevertheless, some aspects of medical usage of this nanomaterials such as problems of safety for human and environment are still need further profound research.

References

1. *Духин А. С., Ульберг З. Р., Карамушка В. И., Овчаренко Ф. Д.* О внешней функции трансмембранного потенциала // Биологические мембраны. – 1989 – Т. 6, № 9 – С. 987–994.
2. *Карамушка В. И., Ульберг З. Р. Грузина Т. Г.* Роль мембранных процессов в накоплении золота Au (III) и Au (0) бактериями // Укр. биохим. журн. – 1990. – Т. 62. – Вып. 1 – С. 76–82.
3. *Карамушка В. И., Ульберг З. Р., Грузина Т. Г., Степура Л. Г.* Функциональная гетерогенность клеточной поверхности как фактор гетерокоагуляции микробных клеток и минеральных частиц // Коллоид. журн. – 1998. – Т. 60, № 3 – С. 327–330.

4. *Ульберг З. Р., Карамушка В. И., Грузина Т. Г.* и др. Влияние протонофоров на гетерокоагуляцию бактериальных клеток и минеральных частиц // Коллоидн. журн. – 1990. – № 1 – С. 172–178.
5. *Ульберг З. Р., Подольская В. И., Карамушка В. И.* и др. Взаимодействие белков с частицами коллоидного золота. Флокуляция белками золей золота // Коллоид. журн. – 1986. – Т. 48, № 5. – С. 1038–1042.
6. *Ahamed M., Karns M., Goodson M.* et al. DNA damage response to different surface chemistry of silver nanoparticles in mammalian cells // Toxicology and Applied Pharmacology. – 2008. – Vol. 233, N 3. – P. 404–410.
7. *Akymenko L. I., Reznichenko L. S., Gruzina T. G.* et al. Metal nanoparticles as perspective activators of probiotic preparations' biological effects", Abstracts of Ukrainian-German Symposium on Physics and Chemistry of Nanostructures and on Nanobiotechnology (Beregove, September 6–10). – The Crimea, Ukraine – 2010 – P. 239.
8. *Alexander J. W.* History of the medical use of silver // Surgical Infections – 2009 – Vol. 3 – P. 289–299.
9. *An K., Hyeon T.* Synthesis and biomedical applications of hollow nanostructures // Nano Today. – 2009. – Vol. 4, N 4. – P. 359–373.
10. *Arora S., Jain J., Rajwade J. M., Paknikar K. M.* Interactions of silver nanoparticles with primary mouse fibroblasts // Toxicology and Applied Pharmacology. – 2009. – Vol. 236. – P. 310–318.
11. *Aruguete D. M., Hochella M. F.* Bacteria–nanoparticle interactions and their environmental implications // Environmental Chemistry. – 2010. – Vol. 7, N 1. – P. 3–9.
12. *Asharani P. V.* Cytotoxicity and genotoxicity of silver nanoparticles in human cells // ACS Nano. – 2009. – Vol. 3, N 2. – P. 279–290.
13. *Banaee M. G., Crozier K. B.* Gold nanorings as substrates for surface-enhanced Raman scattering // Optics Letters. – 2010. – Vol. 35, N 5. – P. 760–762.
14. *Banerjee I. A., Yu L., Matsui H.* Cu nanocrystal growth on peptide nanotubes by biomineralization: size control of Cu nanocrystals by tuning peptide conformation // Proceedings of the National Academy of Sciences of the United States of Am. – 2003. – Vol. 100, N 25. – P. 14678–14682.
15. *Banerji S. K., Hayes M. A.* Examination of nonendocytotic bulk transport of nanoparticles across phospholipid membranes // Langmuir. – 2007. – Vol. 23, N 6. – P. 3305–3313.
16. *Baptista P., Pereira E., Eaton P. et al.* Gold nanoparticles for the development of clinical diagnosis methods // Analytical and Bioanalitycal Chemistry. – 2008. – Vol. 391, N 3. – P. 943–950.
17. *Baram-Pinto D., Shukla S., Perkas N.* et al. Inhibition of herpes simplex virus type 1 infection by silver nanoparticles capped with mercaptoethane sulfonate // Bioconjugate Chemistry. – 2009. – Vol. 20, N 8. – P. 1497–1502.
18. *Baun A., Hartmann N. B., Grieger K., Kusk K. O.* Ecotoxicity of engineered nanoparticles to aquatic invertebrates: a brief review and recommendations for future toxicity testing // Ecotoxicology. – 2008. – Vol. 17, N 5. – P. 387–395.
19. *Bayati M., Patoka P., Giersig M.,. Savinova E. R* An approach to fabrication of metal nanoring arrays // Langmuir. – 2010. – Vol. 26, N 5. – P. 3549–3554.
20. *Bhattacharaya R., Mukherjee P.* Biological properties of naked" metal nanoparticles // Advanced Drug Delivery Reviews. – 2008. – Vol. 60. – P. 1289–1306.
21. *Bhol K. C., Alroy J., Schechter P. J.* Anti-inflammatory effect of topical nanocrystalline silver cream on allergic contact dermatitis in a guinea pig model // Clin. and Experiment. Dermatol. – 2004. – Vol. 26, N 3. – P. 282–287.
22. *Bhol K. C., Shechter P. J.* Effects of nanocrystalline silver (NPI 32101) in a rat model of ulcerative colitis // Digestive Diseases and Sciences. – 2007. – Vol. 52. – P. 2732–2742.
23. *Bilberg K., Malte H., Wang T., Baatrup E.* Silver nanoparticles and silver nitrate cause respiratory stress in Eurasian perch (Perca fluviatilis) // Aquatic toxicology. – 2010. – Vol. 96. – P. 159–165.
24. *Borkow G., Gabbay J.* Copper as a biocidal tool // Current Med. l Chemistry. – 2005. – Vol. 12, N 18. – P. 2163–2175.
25. *Borkow G., Gabbay J. Copper* An Ancient Remedy Returning to Fight Microbial, Fungal and Viral Infections // Current Chemical Biology. – 2009. – Vol. 3, N 3. – P. 272–278.
26. *Borkow G., Lara H. H., Covington C. Y.* et al. Deactivation of human immunodeficiency virus type 1 in medium by copper oxide-containing filters // Antimicrobial Agents and Chemotherapy. – 2008. – Vol. 52, N 2. – P. 518–525.
27. *Borkow G., Zhou S. S., Page T., Gabbay J.* A novel anti-influenza copper oxide containing respiratory face mask // PLoS One. – 2010. – Vol. 5, N 6. – P. e11295.
28. *Briley-Saebo K., Bjørnerud A., Grant D. et al.* Hepatic cellular distribution and degradation of iron oxide nanoparticles following single intravenous injection in rats: implications for magnetic resonance imaging // Cell and Tissue Research. – 2004. – Vol. 316, N 3. – P. 315–323.

29. *Cao Y., Wu X, Wang M.* Silver nanoparticles fluorescence enhancement effect for determination of nucleic acids with kaempferol-Al(III) // Talanta. – 2011. – Vol. 84, N 4. – P. 1188–1194.
30. *Chang Y., Teo J. J., Zeng H. C.* Formation of colloidal CuO nanocrystallites and their spherical aggregation and reductive transformation to hollow Cu2O nanospheres // Langmuir. – 2005. – Vol. 21, N 3. – P. 1074–1079.
31. *Chen J., Wiley B. J., Xia Y.* One-dimensional nanostructures of metals: large-scale synthesis and some potential applications // Langmuir. – 2007. – Vol. 23, N 8. – P. 4120–4129.
32. *Cheng R., Zhou W., Wang J. L.* et al. Dechlorination of pentachlorophenol using nanoscale Fe/Ni particles: role of nano-Ni and its size effect // J. of Hazardous Materials. – 2010 – Vol. 180, N 1–3. – P. 79–85.
33. *Cho W. S., Cho M., Jeong J.* et al. Acute toxicity and pharmacokinetics of 13 nm-sized PEG-coated gold nanoparticles // Toxicol. Appl. Pharmacol. – 2009. – Vol. 236, N 1. – P. 16–24.
34. *Choi H. S., Liu W., P. Misra* et al. Renal clearance of nanoparticles // Nature Biotechnology. – 2007. – Vol. 25, N 10. – P. 1165–1170.
35. *Choi O., Hu Z.* Size dependent and reactive oxygen species related nanosilver toxicity to nitrifying bacteria // Environmental Science & Technology. – 2008. – Vol. 42, N 12. – P. 4583–4588.
36. *Chopra I.* The increasing use of silver-based products as antimicrobial agents: a useful development or a cause of concern?" // J. of Antimicrobial Chemotherapy. – 2007. – Vol. 59. – P. 587–590.
37. *Chourpa I., Douziech-Eyrolles L., Ngaboni-Okassa L.* et al. Molecular composition of iron oxide nanoparticles, precursors for magnetic drug targeting, as characterized by confocal Raman microspectroscopy // Analyst. – 2005. – Vol. 130, N 10. – P. 1395–1403.
38. *Clark K. A., White R. H., Silbergeld E. K.* Predictive models for nanotoxicology: Current challenges and future opportunities // Regulatory Toxicology and Pharmacology – 2011 – Vol. 59, N 3 – P. 361–363.
39. *Demir E., Vales G., Kaya B. E.* et al. Genotoxic analysis of silver nanoparticles in Drosophila // Nanotoxicology. – 2011. doi:10.3109/17435390.2010.529176.
40. *Diao M., Yao M.* Use of zero-valent iron nanoparticles in inactivating microbes // Water Research. – 2009. – Vol. 43, N 20. – P. 5243–5251.
41. *Dukhin A. S.* Biospecific mechanism of double layer formation and peculiarities of cell electrophoresis"// Colloids Surf A. – 1993. – Vol. 73. – P. 29–48.
42. *Dukhin A. S., Karamushka V. I.* Biospecifical mechanism of the living cell double layer formation", Abstr. of 7th Int. Conf. Surface and Colloid Science // Compiegne, France. – 1991. – Vol. 3. – P. 357.
43. *Dukhin A. S., Karamushka V. I., Ulberg Z. R., Abidor I. G.* On the existence of an intramembrane field stabilization system in cells" // Bioelectrochem Bioenerg. – 1991. – Vol. 26, N 2. – P. 131–138.
44. *Dukhin A., Ulberg Z., Karamushka V., Gruzina T.* Peculiarities of live cells' interaction with micro- and nanoparticles, Advances in Colloid and Interface Science. – 2010. – Vol. 159. – P. 60–71.
45. *Dunn K., Edwards-Jones V.* The role of ActicoatTM with nanocrystalline silver in the management of burns // Burns. – 2004. – Vol. 30 – P. 1–9.
46. *Dybkova S., Romanko M., Gruzina T.* et al. Gold nanoparticles genotoxicity" // Ukr. Biochem. J. – 2009. – Vol. 81, N 4 – P. 291.
47. *Dybkova S. N., Rieznichenko L. S., Gruzina T. G.* et al. Risk assessment of nanomaterials by systems' biomarkers", Abstracts of Ukrainian-German Symposium on Physics and Chemistry of Nanostructures and on Nanobiotechnology (Beregove, September 6–10). – The Crimea, Ukraine, 2010. – P. 227.
48. *Elechiguerra J. L., Burt J. L., Morones J. R. et al.* Interaction of silver nanoparticles with HIV-1 // J. of Nanobiotechnology. – 2005. – Vol. 3, N 6.
49. *Elliott D. W., Lien H. L., Zhang W. X.* Zerovalent iron nanoparticles for treatment of ground water contaminated by hexachlorocyclohexanes // J. of Environmental Quality. – 2008. – Vol. 37, N 6. – P. 2192–2201.
50. *El-Sayed H., Huang X., El-Sayed M. A.* Selective laser photothermal therapy of epithelial carcinoma using anti-EGFR antibody conjugated gold nanoparticles // Cancer letters. – 2006. – Vol. 239, N 1. – P. 129–135.
51. *Fayaz A. M., Balaji K., Girilal M.* et al. Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria // Nanomedicine. – 2010. – Vol. 6, N 1. – P. 103–109.
52. *Ferapontova E. E., Olsen E. M., Gothelf K. V.* An RNA Aptamer-Based Electrochemical Biosensor for Detection of Theophylline in Serum // J. of Am. Chemical Society. – 2008. – Vol. 130, N 13. – P. 4256–4258.

53. *Figuerola A., Di Corato R., Manna L., Pellegrino T.* From iron oxide nanoparticles towards advanced iron-based inorganic materials designed for biomedical applications // Pharmaceutical Research. – 2010. – Vol. 62, N 2. – P. 126–143.
54. *Foldbjerg R., Dang D. A., Autrup H.* Cytotoxicity and genotoxicity of silver nanoparticles in the human lung cancer cell line, A549" // Archives of toxicology – 2010. doi: 10.1007/s00204-010-0545-5.
55. *Gant V. A., Wren M. W. D., Rollins M. S. M.* et al. Three novel highly charged copper-based biocides: safety and efficacy against healthcare-associated organisms // J. of Antimicrobial Chemotherapy. – 2007. – Vol. 60, N 2. – P. 294–299.
56. *Gao J., Liang G., Cheung J. S.* et al. Multifunctional yolk-shell nanoparticles: a potential MRI contrast and anticancer agent // J. of the Am. Chemical Society. – 2008. – Vol. 130, N 35. – P. 11828–11833.
57. *Gao J., Liang G., Zhang B.* et al. FePt@CoS(2) yolk-shell nanocrystals as a potent agent to kill HeLa cells // J. of the Am. Chemical Society. – 2007. – Vol. 129, N 5. – P. 1428–1433.
58. *Geraldes C. F., Laurent S.* Classification and basic properties of contrast agents for magnetic resonance imaging // Contrast Media & Molecular Imaging. – 2009. – Vol. 4, N 1. – P. 1–23.
59. *Gou N., Onnis-Hayden A., Gu A. Z.* Mechanistic toxicity assessment of nanomaterials by whole-cell-array stress genes expression analysis // Environmental Science and Technology. – 2010. – Vol. 44, N 15. – P. 5964–5970.
60. *Grass G., Rensing C., Solioz M.* Metallic copper as an antimicrobial surface // Applied and Environmental Microbiology. – 2011. – Vol. 77, N 5. – P. 1541–1547.
61. *Griffitt R. J., Luo J., Gao J.* et al. Effects of particle composition and species on toxicity of metallic nanomaterials in aquatic organisms" // Environmental Toxicology and Chemistry. – 2008. – Vol. 9. – P. 1972–1978.
62. *Guigas G., Kalla C., Weiss M.* Probing the nanoscale viscoelasticity of intracellular fluids in living cells // Biophysical J. – 2007. – Vol. 93, N 1. – P. 316–323.
63. *Guo S., Huang Y.,Jiang Q. et al.* Enhanced gene delivery and siRNA silencing by gold nanoparticles coated with charge-reversal polyelectrolyte // ACS Nano. – 2010. – Vol. 4, N 9. – P. 5505–5511.
64. *Haas I., Shanmugam S., Gedanken A.* Pulsed sonoelectrochemical synthesis of size-controlled copper nanoparticles stabilized by poly(N-vinylpyrrolidone) // The J. of Physical Chemistry B. – 2006. – Vol. 110, N 34. – P. 16947–16952.
65. *Hahn P. F., Stark D. D., Lewis J. M.* et al. First clinical trial of a new superparamagnetic iron oxide for use as an oral gastrointestinal contrast agent in MR imaging // Radiology. – 1990. – Vol. 175, N 3. – P. 695–700.
66. *Hainfeld J. F., Dilmanian F. A., Zhong Z.* et al. Gold nanoparticles enhance the radiation therapy of a murine squamous cell carcinoma // Physics in Med. and Biology. – 2010. – Vol. 55, N 11. – P. 3045–3059.
67. *Hoppener C., Novotny L.* Antenna-based optical imaging of single Ca2+ transmembrane proteins in liquids // Nano Letters. – 2008. – Vol. 8, N 2. – P. 642–646.
68. *Hou S. Y., Chen H. K., Cheng H. C., Huang C. Y.* Development of zeptomole and attomolar detection sensitivity of biotin-peptide using a dot-blot gold nanoparticle immunoassay // Analytical Chemistry. – 2007. – Vol. 79, N 3. – P. 980–985.
69. *Hsiao J. K., Chu H. H., Wang Y. H. et al.* Macrophage physiological function after superparamagnetic iron oxide labeling // NMR Biomed. – 2008. – Vol. 21, N 8. – P. 820–829 [http://www.sciencedirect.com/science/article/pii/S0887233311000658]
70. *Hu M., Qian L., Briñas R. P.* et al. Gold nanoparticle-protein arrays improve resolution for cryo-electron microscopy // J. of Structural Biology. – 2008. – Vol. 161, N 1. – P. 83–91.
71. *Huang X., El-Sayed I. H., Qian W., El-Sayed M. A.* Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods // J. of Am. Chemical Society. – 2006. – Vol. 128, N 6. – P. 2115–2120.
72. *Huang X., Jain P. K., El-Sayed I. H., El-Sayed M. A.* Plasmonic photothermal therapy (PPTT) using gold nanoparticles // Lasers in Medical Science. – 2008. – Vol. 23, N 3 – P. 217–228.
73. *Hubbs A. F., Mercer R. R., Benkovic S. A.* et al. Nanotoxicology – A Pathologist's Perspective // Toxicologic Pathology. – 2011. – Vol. 39, N 2. – P. 301–324.
74. *Huber D. L., Schwarz J. A., Contescu C. I., Putyera K.* Iron nanoparticles in: Dekker encyclopedia of nanoscience and nanotechnology. – 2008. – Vol. 3. – P. 1681–1687, CRC Press, Taylor and Francis Group, Boca Raton, FL.
75. *Hume D. A., Ross I. L., Himes S. R.* et al. The mononuclear phagocyte system revisited // J.of Leukocyte Biology. – 2002. – Vol. 72, N 4. – P. 621–627.
76. *Jain J., Arora S., Rajwade J. M.* et al. Silver nanoparticles in therapeutics: development of an antimicrobial gel formulation for topical use // Molecular Pharmaceutics. – 2009. – Vol. 6, N 5. – P. 1388–1401.

77. *Jain K. K.* Nanodiagnostics: application of nanotechnology in molecular diagnostics // Expertert Review of Molecular Diagnostics. – 2003. – Vol. 3, N 2. – P. 153–161.
78. *Jain P. K., Lee K. S., El-Sayed I. H., El-Sayed M. A.* Calculated absorption and scattering properties of gold nanoparticles of different size, shape, and composition: applications in biological imaging and biomedicine // J. of Physical Chemistry. – 2006. – Vol. 110, N 14. – P. 7238–7248.
79. *Ji J. H., Jung J. H., Kim S. S.* et al. Twenty-eight-day inhalation toxicity study of silver nanoparticles in Sprague-Dawley rats // Inhalation Toxicology. – 2007. – Vol. 19, N 10. – P. 857–871.
80. *Joo S. H., Feitz A. J., Sedlak D. L., Waite T. D.* Quantification of the oxidizing capacity of nanoparticulate zero-valent iron // Environmental Science & Technology. – 2005. – Vol. 39, N 5. – P. 1263–1268.
81. *Jun Y. W., Seo J. W., Cheon J.* Nanoscaling laws of magnetic nanoparticles and their applicabilities in biomedical sciences // Accounts of Chemical Research. – 2008. – Vol. 41, N 2. – P. 179–189.
82. *Kahru A., Dubourguier H. C.* From ecotoxicology to nanoecotoxicology // Toxicology. – 2010. – Vol. 269, N 2–3. – P. 105–119.
83. *Kandakkathara A., Utkin I., Fedosejevs R.* Surface-Enhanced Raman Scattering (SERS) Detection of Low Concentrations of Tryptophan Amino Acid in Silver Colloid // Applied Spectroscopy. – 2011. – Vol. 65, N 5. – P. 507–513.
84. *Kapoor S., Mukherjee T.* Photochemical formation of copper nanoparticles in poly(N-vinylpyrrolidone) // Chemical Physics Letters. – 2003. – Vol. 370, N 1–2. – P. 83–87.
85. *Karamushka V. I., Ulberg Z. R., Gruzina T. G., Dukhin A. S.* ATP-dependent gold accumulation by Chlorella living cells" // Acta Biotechnol. – 1991. – Vol. 11, N 3. – P. 197–203.
86. *Kawanishi S., Hiraku Y., Oikawa S.* Mechanism of guanine-specific DNA damage by oxidative stress and its role in carcinogenesis and aging // Mutation Research.. – 2001 – Vol. 488, N 1. – P. 65–76.
87. *Khan M. A., Hogan T. P., Shanker B.* Metallic nanorods synthesis and application in surface enhanced Raman spectroscopy // J. of Nano Systems & Technology. – 2009. – Vol. 1, N 1. – P. 1–11.
88. *Kim J. Y., Park H. J., Lee C.* et al. Inactivation of Escherichia coli by nanoparticulate zerovalent iron and ferrous ion // Applied and Environmental Microbiology. – 2010. – Vol. 76, N 2. – P. 7668–7670.
89. *Kim S., Choi J. E., Choi J.* et al. Oxidative stress-dependent toxicity of silver nanoparticles in human hepatoma cells // Toxicology In Vitro. – 2009. – Vol. 23, N 6. – P. 1076–1084.
90. *Kim Y. S., Kim J. S., Cho H. S.* et al. Twenty-eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in Sprague-Dawley rats // Inhalation Toxicology. – 2008. – Vol. 20, N 6. – P. 575–583.
91. *Kneipp J., Kneipp H., Wittig B., Kneipp K.* One- and two-photon excited optical ph probing for cells using surface-enhanced raman and hyper-raman nanosensors // Nano Letters. – 2007. – Vol. 7, N 9. – P. 2819–2823.
92. *Kong H., Jang J.* Synthesis and antimicrobial properties of novel silver/polyrhodanine nanofibers // Biomacromolecules. – 2008. – Vol. 9. – P. 2677–2681.
93. *Kooi M. E., Cappendijk V. C., Cleutjens K. B.* et al. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging // Circulation. – 2003. – Vol. 107, N 19. – P. 2453–2458.
94. *Krupanidhi S., Sreekumar A., Sanjeevi C. B.* Copper & biological health // Indian Journal of Medical Research. – 2008. – Vol. 128, N 4. – P. 448–461.
95. *Kumari M., Mukherjee A., Chandrasekaran N.* Genotoxicity of silver nanoparticles in Allium cepa // Science of the Total Environment. – 2009. – Vol. 407, N 7. – P. 5243–5246.
96. *Laban G., Nies L. F., Turco R. F.* et al. The effects of silver nanoparticles on fathead minnow (Pimephales promelas) embryos // Ecotoxicology. – 2010. – Vol. 19. – P. 185–195.
97. *Lara H. H., Ayala-Nuñez N. V., Ixtepan-Turrent L., Rodriguez-Padilla C.* Mode of antiviral action of silver nanoparticles against HIV-1 // J. Nanobiotechnology. – 2010. – Vol. 8, N1.
98. *Lara H. H., Ixtepan-Turrent L., Garza-Treviño E. N., Rodriguez-Padilla C.* PVP-coated silver nanoparticles block the transmission of cell-free and cell-associated HIV-1 in human cervical culture // J. of Nanobiotechnology. – 2010. – Vol. 8, N 15.
99. *Laurent S., Forge D., Port M. et al.*Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications // Chemical Reviews. – 2008. – Vol. 108, N 6. – P. 2064–2110.
100. *Lee C., Kim J. Y., Lee W.* et al. Sedlak Bactericidal effect of zero-valent iron nanoparticles on Escherichia coli // Environmental Science & Technology. – 2008. – Vol. 42, N 13. – P. 4927–4933.

101. *Lee K. S., El-Sayed M. A.* Gold and silver nanoparticles in sensing and imaging: sensitivity of plasmon response to size, shape, and metal composition // The J. of Physical Chemistry B. – 2006. – Vol. 110, N 39. – P. 19220–19225.
102. *Li L., Hu Q., Zeng J., Qi H., Zhuang G.* Resistance and biosorption mechanism of silver ions by Bacillus cereus biomass // J. of Environmental Sciences (China). – 2011. – Vol. 23, N 1. – P. 108–111.
103. *Li Q., Mahendra D., Lyon D., Brunet L.* et al. Antimicrobial nanomaterials for water disinfection and microbial control: Potential applicatons and implications // Water research. – 2008. – Vol. 42. – P. 4591–4602.
104. *Li W., Salanitri J., Tutton S., Dunkle E. E.* et al. Lower extremity deep venous thrombosis: evaluation with ferumoxytol-enhanced MR imaging and dual-contrast mechanism – preliminary experience // Radiology. – 2007. – Vol. 242, N 3. – P. 873–881.
105. *Li X. Q., Zhang W. X.* Iron nanoparticles: the core-shell structure and unique properties for Ni (II) sequestration // Langmuir. – 2006. – Vol. 22, N 10. – P. 4638–4642.
106. *Li X., Elliott D. W., Zhang W.* Zero-valent iron nanoparticles for abatement of environmental pollutants: materials and engineering aspects // Critical Reviews in Solid State and Materials Sciences. – 2006. – Vol. 31, N 4. – P. 111–122.
107. *Liu H. F., Liu Z. L., Xie C. S.* et al. The antifertility effectiveness of copper/low-density polyethylene nanocomposite and its influence on the endometrial environment in rats // Contraception. – 2007. – Vol. 75, N 2. – P. 157–161.
108. *Lu L., Sun R.W., Chen R.* et al. Silver nanoparticles inhibit hepatitis B virus replication // Antiviial Therapy. – 2008. – Vol. 13, N 2. – P. 253–262.
109. *Luna V. A., Hall T. J., King D. S., Cannons A. C.* Susceptibility of 169 USA300 methicillin-resistant Staphylococcus aureus isolates to two copper-based biocides, CuAL42 and CuWB50 // J. of Antimicrobial Chemotherapy. – 2010. – Vol. 65, N 5. – P. 939–941.
110. *MacIsaac L., Espey E.* Intrauterine contraception: the pendulum swings back // Obstetrics and Gynecology Clin. of North Am. – 2007. – Vol. 34, N 1.. – P. 91–111.
111. *Madhumanthi K., Sudsheesh Kumar P. T., Abhilash S.* et al. Development of novel chitin/nanosilver composite scaffolds for wound dressing applications // J. of Material Science. Materials in Med. – 2010. – Vol. 21, N 2. – P. 807–813.
112. *Madl A. K., Pinkerton K. E.* Health effects of inhaled engineered and incidental nanoparticles // Critical Reviews in Toxicology. – 2009. – Vol. 39, N 8. – P. 629–658.
113. *Manna P., Ghosh M., Ghosh J.* et al. Contribution of nano-copper particles to in vivo liver dysfunction and cellular damage: Role of I B /NF- B, MAPKs and mitochondrial signal // Nanotoxicology (In press.).
114. *Martin J. E., Herzing A. A., Yan W.* Determination of the oxide layer thickness in core-shell zerovalent iron nanoparticles // Langmuir. – 2008. – Vol. 24, N 8. – P. 4329–4334.
115. *Miura N., Shinohara Y.* Cytotoxic effect and apoptosis induction by silver nanoparticles in HeLa cells // Biochemical and Biophysical Communications. – 2009. – Vol. 309. – P. 733–737.
116. *Moghimi S. M. , Hunter A. C. , Murray J. C.* Long-circulating and target-specific nanoparticles: theory to practice // Pharmacological Reviews. – 2001. – Vol. 53, N 2. – P. 283–318 [http://www.sciencedirect.com/science/article/pii/S0887233311000658]
117. *Moghimi S. M., Hunter A. C.* Recognition by macrophages and liver cells of opsonized phospholipid vesicles and phospholipid headgroups // Pharmaceutical Research. – 2001. – Vol. 18, N 1. – P. 1–8.
118. *Müller K., Skepper J. N., Posfai M.* et al. Effect of ultrasmall superparamagnetic iron oxide nanoparticles (Ferumoxtran-10) on human monocyte-macrophages in vitro // Biomaterials. – 2007. – Vol. 28, N 9. – P. 1629–1642.
119. *Nair P. M., Park S. Y., Lee S.W., Choi J.* Differential expression of ribosomal protein gene, gonadotrophin releasing hormone gene and Balbiani ring protein gene in silver nanoparticles exposed Chironomus riparius // Aquatic Toxicology. – 2011. – Vol. 101, N 1. – P. 31–37.
120. *Noblitt S. D., Huehls A. M., Morris D. L.* The role of metal ion binding in generating 8-hydroxy-2'-deoxyguanosine from the nucleoside 2'-deoxyguanosine and the nucleotide 2'-deoxyguanosine-5'-monophosphate // J. of Inorganic Biochemistry. – 2007. – Vol. 101, N 3. – P. 536–542.
121. *Norman R. S., Stone J. W., Gole A.* et al. Targeted photothermal lysis of the pathogenic bacteria, Pseudomonas aeruginosa, with gold nanorods // Nano Letters. – 2008. – Vol. 8, N 1. – P. 302–306.
122. *Ordzhonikidze G., Ramaiyya L. K., Egorova E. M., Rubanovich A.V.* Genotoxic effects of silver nanoparticles on mice in vivo // Acta naturae. – 2009. – N 3. – P. 99–101.

123. *Oyelere K., Chen P. C., Huang X.* et al. Peptide-conjugated gold nanorods for nuclear targeting // Bioconjugate Chemistry. – 2007. – Vol. 18, N 5. – P. 1490–1497.
124. *Pal S., Tak K. Y., J. M. Song* Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium Escherichia coli // Applied and environmental Microbiology. – 2007. – Vol. 73. N 6. – P. 1712–1720.
125. *Pan Y., Neuss S., Leifert M.* et al. Size-dependent cytotoxicity of GNPs // Small. – 2007. – Vol. 3. – P. 1941–1949.
126. *Panda K. K., Achary V. M., Krishnaveni R.* et al. In vitro biosynthesis and genotoxicity bioassay of silver nanoparticles using plants // Toxicology In Vitro. – 2011.
127. *Panyala N. R., Peña-Méndez E. M., Havel J.* Gold and nano-gold in medicine: overview, toxicology and perspectives // J. Appl. Biomed. – 2009. – Vol. 7. – P. 75–91.
128. *Phenrat T., Long T. C., Lowry G. V., Veronesi B.* Partial oxidation (aging") and surface modification decrease the toxicity of nanosized zerovalent iron // Environmental Science & Technology. – 2009. – Vol. 43, N 1. – P. 195–200.
129. *Pouponneau P., Leroux J. C., Soulez G.* et al. Co-encapsulation of magnetic nanoparticles and doxorubicin into biodegradable microcarriers for deep tissue targeting by vascular MRI navigation // Biomaterials. – 2011. – Vol. 32 N 13. – P. 3481–3486.
130. *Reisse J., Francois H., Vandercammen J.* et al. Sonoelectrochemistry in aqueous electrolyte: A new type of sonoelectroreactor // Electrochimica Acta. – 1994. – Vol. 39, N 1. – P. 37–39.
131. *Rezaei B., Majidi N., Rahmani H., Khayamian T.* Electrochemical impedimetric immunosensor for insulin like growth factor-1 using specific monoclonal antibody-nanogold modified electrode // Biosensensors & Bioelectronics. – 2011. – Vol. 26, N 5. – P. 2130–2134.
132. *Reznichenko L., Gruzina T., Vember V., Ulberg Z.*Gold nanoparticles size-dependent interaction with prokaryotic and eukaryotic cancer cells", Abstracts of German-Ukrainian Symposium on Nanoscience and Nanotechnology (Essen, September 22–25). – Germany, 2008 – P. 143.
133. *Rieznichenko L., Dybkova S., Gruzina T.* et al. Gold nanoparticles size- and concentration dependent influence on cancer cells", Abstracts of E-MRS Spring meeting (Strasbourg, June 8–12). – France, Strasbourg, 2009.
134. *Rieznichenko L., Shpyleva S., Gruzina T.* et al. Biochemical mechanisms of gold nanoparticles influence: significance for biotechnology and medicine"// Ukr. Biochem. J. – 2009. – Vol. 81, N 4. – P. 244.
135. *Sahoo S., Husale S., Colwill B.* et al. Electric field directed self-assembly of cuprous oxide nanostructures for photon sensing // ACS Nano. – 2009. – Vol. 3, N 12. – P. 3935–3944.
136. *Saleh A., Schroeter M., Jonkmanns C.* et al. In vivo MRI of brain inflammation in human ischaemic stroke // Brain. – 2004. – Vol. 127, N 7. – P. 1670–1677.
137. *Salou C., Jamme F., Maranges C.* et al. Synchrotron FTIR microspectroscopy of the yeast Saccharomyces cerevisiae after exposure to plasma-deposited nanosilver-containing coating" Analytical and Bioanalytical // Chemistry. – 2010. – Vol. 396. – P. 1441–1450.
138. *Samberg M. E., Oldenburg S. J., Monteiro-Riviere N. A.* Evaluation of silver nanoparticle toxicity in skin in vivo and keratinocytes in vitro // Environmental Health Perspectives. – 2009. – Vol. 118, N 3. – P. 407–413.
139. *Schwenk M. H.* Ferumoxytol: a new intravenous iron preparation for the treatment of iron deficiency anemia in patients with chronic kidney disease // Pharmacotherapy. – 2010. – Vol. 30, N 1. – P. 70–79.
140. *Selvan S. T., Patra P. K., Ang C. Y., Ying J. Y.* Synthesis of silica-coated semiconductor and magnetic quantum dots and their use in the imaging of live cells // Angewandte Chemie International Edition Engl. – 2007 – Vol. 46, N 14. – P. 2448–2452.
141. *Service R. F.* DNA assembles materials from the ground up // Science. – 2008. – Vol. 319, N 5863. – P. 558–559.
142. *Son S. J., Bai X., Lee S. B.* Inorganic hollow nanoparticles and nanotubes in nanomedicine. Part 2: Imaging, diagnostic, and therapeutic applications // Drug. Discovery Today. – 2007. – Vol. 12, N 15–16. – P. 657–663.
143. *Speshock J. L., Murdock R. C., Braydich-Stolle L. K. et al.* Interaction of silver nanoparticles with Tacaribe virus // J. of Nanobiotechnology. – 2010. – Vol. 8, N 19.
144. *Stevens K. N., Croes S., Boersma R. S. et al.* Hydrophilic surface coatings with embedded biocidal silver nanoparticles and sodium heparin for central venous catheters // Biomaterials. – 2011. – Vol. 32, N 5. – P. 1264–1269.

145. *Su B., Tang D., Li Q.* et al. Gold-silver-graphene hybrid nanosheets-based sensors for sensitive amperometric immunoassay of alpha-fetoprotein using nanogold-enclosed titania nanoparticles as labels // Analytica Chimica Acta. – 2011. – Vol. 692, N 1–2. – P. 116–124.
146. *Sun X., Rossin R., Turner J. L. et al.* An assessment of the effects of shell cross-linked nanoparticle size, core composition, and surface PEGylation on in vivo biodistribution // Biomacromolecules. – 2005. – Vol. 6, N 5. – P. 2541–2554.
147. *Sung J. H., Ji J. H., Park J. D.* et al. Subchronic inhalation toxicity of silver nanoparticles" // Toxicological sciences. – 2009. – Vol. 108, N 2. – P. 452–461.
148. *Tang D., Tang J., Su B.* et al. Chen Simultaneous determination of five-type hepatitis virus antigens in 5 min using an integrated automatic electrochemical immunosensor array // Biosensensors & Bioelectronics. – 2010. – Vol. 25, N 7. – P. 1658–1662.
149. *Tang J., Zhou L., Gao W.* et al. Visual DNA microarrays for simultaneous detection of human immunodeficiency virus type-1 and Treponema pallidum coupled with multiplex asymmetric polymerase chain reaction // Diagnostic Microbiology and Infectious. Disease. – 2009. – Vol. 65, N 4. – P. 372–378.
150. *Tang Y.,Jiang C., Liang A.* et al. A new atomic absorption spectral assay for the determination of trace IgG using immunonanogold // Bioprocess Biosystystems Engineering. – 2011. – Vol. 34, N 4. – P. 471–476.
151. *Thaxton C. S., Georganopoulou D. G., Mirkin C. A.* Gold nanoparticle probes for the detection of nucleic acid targets // Clinica Chimica Acta. – 2006. – Vol. 363, N 1–2. – P. 120–126.
152. *Tran N., Mir A., Mallik D.* et al. Bactericidal effect of iron oxide nanoparticles on Staphylococcus aureus // International J. of Nanomedicine. – 2010. – Vol. 5 – P. 277–283.
153. *Ulberg Z. R., Karamushka V. I., Vidybida A. K.* et al. Interaction of energized bacteria cells with particles of colloidal gold: peculiarities and kinetic model of the process" // Biochim. Biophys. Acta. – 1992. – Vol. 1134. – P. 89–95.
154. *Ulberg Z. R., Gruzina T. G., Pertsov N. V.* Colloidal Chemical Properties of Biological Nanosystems // Biomembranes. – 2010. – P. 269–306 (In Nanoscience. Colloidal and Interfacial Aspects"/ ed. by Victor M. Starov: CRC Press Taylor & Francis Group. – Boca Raton, 1216 p.).
155. *Vakarelski I. U., Brown S. C., Higashitani K., Moudgil B. M.* Penetration of living cell membranes with fortified carbon nanotube tips // Langmuir. – 2007. – Vol. 23, N 22. – P. 10893–10896.
156. *Walton B. L., Leja M., Vickers K. C.* et al. Delivery of negatively charged liposomes into the atheromas of Watanabe heritable hyperlipidemic rabbits // Vasc. Med. – 2010. – Vol. 15, N 4. – P. 307–313.
157. *Weaver L., Noyce J. O., Michels H. T., Keevil C. W.* Potential action of copper surfaces on methicillin-resistant Staphylococcus aureus // J. of Applied Microbiology. – 2010. – Vol. 109, N 6. – P. 2200–2205.
158. *Weissleder R., Stark D. D., Engelstad B. L* et al. Superparamagnetic iron oxide: pharmacokinetics and toxicity // Am. J. of Roentgenology. – 1989. – Vol. 152, N 1. – P. 167–173.
159. *Willard M. A., Kurihara L. K., Carpenter E. E.* et al. Chemically prepared magnetic nanoparticles" in: Encyclopedia of nanoscience and nanotechnology, H. S. Nalwa, Ed. – 2004 – Vol. 1 – P. 815–848, Am. Scientific Publishers, Valencia, CA.
160. *Wise J.P., Goodale B. C., Wise S. S.* et al. Silver nanospheres are cytotoxic and genotoxic to fish cells // Aquatic Toxicology. – 2010. – Vol. 97, N 1. – P. 34–41.
161. *Xu C., Yuan Z., Kohler N.* et al. FePt nanoparticles as an Fe reservoir for controlled Fe release and tumor inhibition // J. of the Am. Chemical Society. – 2009. – Vol. 131, N 42. – P. 15346–15351.
162. *Yan W., Herzing A. A., Li X.Q.* et al. Structural evolution of Pd-doped nanoscale zero-valent iron (nZVI) in aqueous media and implications for particle aging and reactivity // Environmental Science & Technology. – 2010. – Vol. 44, N 11. – P. 4288–4294.
163. *Yao W. T., Yu S. H., Zhou Y.* et al. Formation of uniform CuO nanorods by spontaneous aggregation: Selective synthesis of CuO, Cu2O, and Cu nanoparticles by a solid-liquid phase arc discharge process // The J. of Physical Chemistry B. – 2005. – Vol. 109, N 29. – P. 14011–14016.
164. *Zhang Y. X., Das G. K., Xu R., Tan T. T. Y.* Tb-doped iron oxide: bifunctional fluorescent and magnetic nanocrystals // J. of Materials Chemistry. – 2009. – Vol. 19, N 22. – P. 3696–3703.
165. *Zhao C. M., Wang W. X.* Comparison of acute and chronic toxicity of silver nanoparticles and silver nitrate to Daphnia magna // Environmental Toxicology and Chemistry. – 2011. – Vol. 30, N 4. – P. 885–892.

ПЕРСПЕКТИВИ МЕДИЧНОГО ЗАСТОСУВАННЯ МЕТАЛІЧНИХ НАНОЧАСТИНОК ТА НАНОМАТЕРІАЛІВ

І. С. Чекман, З. Р. Ульберг, Н. О. Горчакова, Т. Ю. Небесна, Т. Г. Грузіна, А. О. Прискока, А. М. Дорошенко, П. В. Сімонов (Київ, Україна)

У статті проаналізовано публікації останніх років, присвячені аспектам медичного застосування металічних наночасток та наноматеріалів. Метали у наноструктурованому вигляді виявляють ряд унікальних хімічних, фізичних, фармакологічних властивостей, що дозволяє використовувати їх у діагностиці, лікуванні та профілактиці хвороб, розробці нових лікарських засобів і удосконаленні традиційних. Разом з тим деякі аспекти впровадження цих наноматеріалів залишаються маловивченими, зокрема токсикологічний.

Ключові слова: нанотехнології, наномедицина, нанофармакологія, металічні наночастинки, наноматеріали.

ПЕРСПЕКТИВЫ МЕДИЦИНСКОГО ПРИМЕНЕНИЯ МЕТАЛЛИЧЕСКИХ НАНОЧАСТИЦ И НАНОМАТЕРИАЛОВ

И. С. Чекман, З. Р. Ульберг, Н. А. Горчакова, Т. Ю. Небесная, Т. Г. Грузина, А. О. Прискока, А. М. Дорошенко, П. В. Симонов (Киев, Украина)

Проанализированы публикации последних лет, посвящённые аспектам медицинского применения металлических наночастиц и наноматериалов. Металлы в наноструктурированном виде проявляют ряд уникальных химических, физических, фармакологических свойств, что позволяет использовать их в диагностике, лечении и профилактике болезней, разработке новых лекарственных средств и усовершенствовании традиционных. Тем не менее некоторые аспекты внедрения этих наноматериалов остаются малоизученными, в частности токсикологический.

Ключевые слова: нанотехнологии, наномедицина, нанофармакология, металлические наночастицы, наноматериалы.

ЕКОЛОГІЧНІ ПРОБЛЕМИ ТА ЗДОРОВ'Я НАЦІЇ

УДК [616.211–008.4+612.017]–053.2]:614.876 Надійшла 11.01.2011

I. YE. KOLPAKOV, V. N. PARKHOMENKO V. YU. VDOVENKO, YE. I. STEPANOVA, D. A. BAZYKA, W. J. KARMAUS, E. R. SVENDSEN (Kyiv, Ukraine; Columbia, USA)

FUNCTIONAL STATE OF THE RESPIRATORY AND IMMUN SYSTEM IN CHILDREN–RESIDENTS OF THE RADIOACTIVE CONTAMINATED TERRITORIES

SI "Research Center for Radiation Medicine of AMS of Ukraine",
University of South Carolina <xrisk@ua.fm>

More then 25 years after the Chernobyl accident, a higher prevalence of bronchial hyperreactivity, reduced lung function, and increased levels of free radicals in exhaled breath condensates (EBC) were observed in children residing in radioactive contaminated territories. Comparing children with different residential radiation background, this study investigated fatty acids of EBC using gas liquid chromatography, counts of B-lymphocyte antigen CD19 in T-cell (CD3) and phagocytotic activity of neutrophils in blood samples. Regarding EBC, we demonstrate that lipid peroxidation was activated, antioxidant properties of pulmonary surfactant were decreased, were detected metabolic disorders of essential fatty acids at the stage of bioregulators–eicosanoids formation. Regarding the immune function of blood cells,