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PACS 87.85.Qr, 87.19.xd

NANOPHYSICS AND ANTIVIRAL THERAPY[1]

A new mechanism of interaction between viruses and nanoparticles is proposed. The mechanism is based on the local-field enhancement effect inherent only in nano-objects and can manifest itself in nanoparticle–virus systems. The basic idea consists in vacuum fluctuations that are always present in any physical system. This mechanism is universal and does not depend on the details of nanoparticle and virus structures, which was confirmed by numerous experiments carried out by us and in other scientific groups. A new method of purification of biofluids from nano-objects such as nanoparticles and viruses is also discussed. The method is based on a selective interaction between nano-objects and either a nanostructured surface, along which a surface plasmon-polariton propagates, or a system of nanothreads, on which a local plasmon-polariton is excited. On the basis of the method proposed for weakening the virus activity due to the action of a suspension of nanoparticles, a new effective way for the production of human leukocytic interferon has been developed and verified experimentally.

K e y w o r d s: plasmon-polariton, nanoparticle–virus systems

1. Introduction

The modern life science becomes more and more interdisciplinary [1–7]. Today, it is already no surprise that an article devoted to physical or chemical aspects of diagnostics and treatment is published in a medical journal [8], or a paper published in a physical journal deals with the DNA electroconductivity [1, 5] or the physical aspects of virology [6, 7]. Nowadays, medicine more and more often applies physical methods to diagnostics and treatment of diseases. For instance, the known effect of surface plasmon–polariton resonance [9–11] was successfully applied to diagnostics of some diseases [12, 13], whereas weak electromagnetic radiation in the radio-frequency range has been used for tens of years as one of the methods to treat a considerable number of diseases.

Together with the development of nanotechnologies, the interest to the use of nanosystems such as nanoparticles, nano-structured surfaces, and so on in medicine and biology, in particular, in medical-biological researches and clinical practice, continues to grow. For example, nanoparticles are used for diagnostics of various diseases [14–16], in studying the biophysical processes in living organisms [3, 17–19], and in developing new methods of treatment [20–23].

In biomedical researches, functionalized semiconductor quantum dots are widely applied as biosensors, when luminescence by a semiconductor is used to detect the localization of quantum dots in biomedical structures [24]. In particular, functionalized CdS and CdSe/ZnS semiconductor quantum dots, whose surface is covered with peptides constructed of amino acids arranged in certain sequences, are used for such purposes [25]. Hence, there emerges a possibility to exactly find where nanoparticle markers are localized in medical-biological objects. The functionalized quantum dots are used for studying the passage of nervous pulses in a system of neurons [17], as well as one of the methods of target-aimed drug delivery with the help of nanocontainers.

[1] The work is published as a debatable one.

Solid-state (mainly, metallic) nanoparticles with their surface so modified that some fixed doses of drugs could be attached to them [26], supramolecular structures with geometrical voids [27], carbon nanotubes, and various fullerenes [28] are applied as nanocontainers. Every of those methods includes a preliminary treatment of the nanoparticle surface with a corresponding molecular preparation. However, from a simple physical reasoning, it follows that the very presence of nanoparticles near the cell membranes or the shells of bacteria and viruses can induce a strong change in their properties. In particular, nanoparticles, when being near viruses, can give rise to a considerable modification of their infectious activity.

Within the last years, there appeared a certain information in the scientific literature concerning the antiviral properties of nanoparticle preparations not modified beforehand with specific compounds that block the activity of viruses. For instance, the antiviral activity of titanium dioxide nanoparticles about 4–5 nm in size against the H3N2 influenza virus was reported [29], with the nanoparticle suspension being added to the suspension of viruses. Electron microscopy studies showed that the nanoparticles stuck to the external virus shell already in 15 min and induced its local destructions, which resulted, in turn, in that viruses lost their infectious ability.

The authors of work [30] reported on the antiviral activity of copper iodide (CuI) nanoparticles rather big in dimensions (of about 160 nm) against the type-A influenza virus (H1N1). The cited authors assert that the antiviral activity of those particles is associated with their generation of hydroxyl radicals, because the radicals block the acceptors of N-acetylcysteine. According to their opinion, it is this phenomenon that results in a decrease of the infectious activity of viruses. Similar communications about antiviral properties of various nanoparticles bring us to an idea about a certain universal mechanism of interaction between nanoparticles and viruses that gives rise to blocking the viral activity.

Since the antiviral activity is observed for a large variety of nanoparticles, it is possible to suppose that a certain physical mechanism not connected with chemical interaction governs all that. Such a mechanism can be based on the interaction between nanoobjects – viruses and nanoparticles – by means of a field. In this work, we analyze just those methods of antiviral therapy that are based on the idea of a field-mediated interaction between nanoparticles and viruses. In so doing, we propose the mechanisms of interaction between nanoparticles and viruses that are universal and do not require that nanoparticles should be preliminarily functionalized.

2. Virology and Physics

Viruses are the smallest infectious agents, which can be reproduced only in a living cell [31–33]. We encounter viruses everywhere in our everyday life. Often, owing to the role of viruses as infectious agents, such "meetings" end dramatically, and we have troubles in the form of diseases. The efforts of virology as a life science in a broad sense are aimed, to a great extent, at seeking for the methods to neutralize the activity of viruses, in particular to enhance immunity, and at developing new methods of antiviral therapy. Today, however, the positive role of viruses is more and more under consideration. They are nanoframes for transport and nanoreactors for catalysis. In gene therapy, viruses are used as vehicles for gene delivery and antibacterial means (the so-called phages that infect bacteria). In this context, the study of physical properties revealed by viruses as formations occupying an intermediate position between living and lifeless objects becomes a challenging scientific task, the solution of which, in due time, can shed light on the problem "What is life?" The research of the structural and mechanical features of viruses [34], their ability to self-organization, and other issues can be a first step in studying the physical properties of viruses. There exist a large variety of viruses different by the way of infection, their specialization with respect to infected cells and organs, and the corresponding geometrical shape (see, e.g., Figs. 5 to 10 in book [31]). Nevertheless, a feature that is common for all viruses can be distinguished; namely, every virus consists of a protein shell (in many cases, its form is close to the spherical one) containing a viral nucleic acid. Such a universality of virus structures enables us to study their electrodynamic properties with the use of simple models such as homogeneous particles of a given shape or particles with a shell.

In this context, the visualization of viruses and viral structures is an important factor. Since the typical dimensions of viruses vary from several tens to several hundreds of nanometers, the basic method of viral microscopy is the electron microscopy [35]. However, the latter is characterized by rather a high-energy influence on the object under consideration and can destroy viruses. Therefore, an issue arises concerning

the application of less destructive visualization techniques, in particular, optical ones.

Progress in the near-field optics within the last years [36,37] resulted in that there appeared a special type of microscopy, near-field scanning microscopy [38–40]. It is based on the scattering of evanescent waves and operates in the subwave-length range. The subwave optical microscopy with a resolution of the order of tens of nanometers can also be developed on the basis of the scattering of surface waves, which are immanently evanescent. In particular, this idea serves as a basis for the method applied to visualize nanoparticles located near a surface, along which a surface plasmon-polariton is propagating [41,42]. For instance, in work [42], a communication was made about the label-free visualization method and the measurements of the dimensions and masses of individual virus particles in a solution using a microscopy that is based on the surface plasmon-polariton resonance effect. In work [43], a simple model was proposed, which allows the experimental results obtained for the visualization of virus particles by using the scattering of surface plasmon-polaritons to be analyzed. In particular, it was shown that, in contrast to the Mie model that predicts the nanoparticle image intensity to be proportional to the cube of the nanoparticle size, this parameter can be proportional to the linear particle dimension; and this relation was observed in experiments (see, e.g., work [41]). Hence, physical methods are applied more and more actively in virology. From this point of view, bearing in mind that the main goal of the science about viruses, nevertheless, consists in searching for optimum methods to affect their virulent properties in order to create effective medicines, it is necessary to consider the features of the interaction between viruses and nanoparticles.

3. Interaction Between Viruses and Nanoparticles

Viruses are from 10 to 500 nm in size. For instance, the characteristic size of adenoviruses amounts to 70–90 nm, and that of HIV is 100 nm. A typical dimension of Herpes simplex virus is equal to 170 nm, and that of influenza virus to 200 nm. In other words, viruses are almost perfect objects for nanophysics.

In addition, every virus particle consists of a stable enough protein shell with the carrier of a viral genome – a viral DNA or RNA – inside it. Therefore, one may expect that the virus as a whole is characterized by rather high polarizabilities, linear and nonlinear ones. In particular, this means that viruses can be regarded as objects for the near-field physics [44]. If a nanoparticle is located near a virus, and if the dimensions of the former are of the order of or smaller than the linear dimensions of the latter, an interaction between them associated with fluctuation fields (an analog of Van der Waals forces) may arise. Moreover, the interaction between a virus and a nanoparticle can be resonant, i.e. the so-called configuration resonance [45–47] can be observed, which ultimately gives rise to the anomalous effective absorption of the energy of external radiation by the system "virus–nanoparticle".

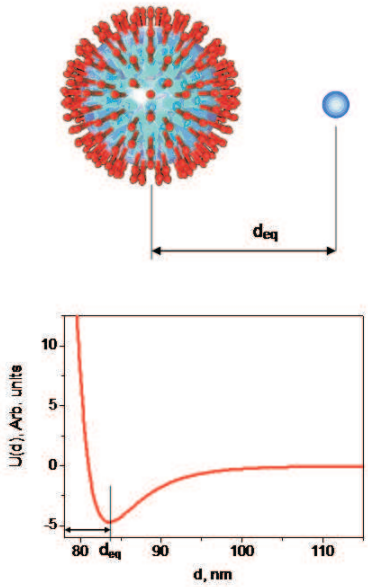

Fig. 1. Schematic diagram of the system "virus–nanoparticle"

This absorption should expectedly stimulate irreversible transformations in the system. For example, weak chemical bonds, which are a component of the receptor formation on the viral capsid, can be destroyed. Thermally induced damages in the virus can take place, because the system "virus–nanoparticle" will be strongly heated up, as the energy of external radiation is absorbed. This means that the illumination of a system with external light can result in that the virus losses its infectious properties. However, another mechanism of neutralization of the virus infection activity can also be realized. The mechanism is connected with the effect of the field of vacuum fluctuations on a virus-nanoparticle system. In order to understand this mechanism better, let us consider the system "virus–nanoparticle" depicted in Fig. 1.

As was shown in work [48], the interaction between nanoparticles characterized by high enough nonlinear polarizabilities can generate a potential that is attractive at large distances, but repulsive at distances of the order of particle dimensions, so that a deep enough potential well is formed (Fig. 1). The potential has rather a complicated profile, but its dependence on the distance between particles can be written down in rather a simple form

$$U(d) = \sum_{n=2,3} \left[\frac{A_n}{d^{6n}} - \frac{B_n}{d^{3n}} \right], \tag{1}$$

where A_n and B_n are coefficients depending on the dimensions and shapes of particles and the substance that they are made of.

Such a potential is formed owing to electric field fluctuations. In work [48], the free energy for a system of particles was written down in the framework of the effective susceptibility approach, and the relevant ground state was found, which corresponded to the emergence of dipole moments at both particles. It is the nonlinear interaction between those dipole moments that results in the formation of potential (1). The profile of this potential is shown in Fig. 1.

A characteristic feature of the potential consists in that its minimum is located at distances of the order of a particle size. Then, in the case where the system is composed of a nanoparticle with the radius of a few nanometers and a virus several tens of nanometers in diameter, the corresponding stable state is formed when the nanoparticle is located at a distance of about 10 nm from the virus shell.

Consider a system "virus–nanoparticle" with interparticle distance of the order of the particle size. Let the nanoparticle undergo the action of electric field fluctuations $E_i^{(0)}(\mathbf{R}_n)$. Then, the dipole moment induced at a particle equals

$$P_i^{(n)}(\mathbf{R}_n) = X_{ij}^{(n)}(\mathbf{R}_n)\, E_j^{(0)}(\mathbf{R}_n), \tag{2}$$

where $X_{ij}^{(n)}(\mathbf{R}_n)$ is the effective susceptibility of the particle, i.e. its electric response to the external field [47]. This susceptibility can be calculated in the framework of pseudovacuum Green's function method [49] so that near-field effects in the system can be taken into consideration. The emerging dipole moment induces the following electric field at the virus:

$$E_i^{(v)}(\mathbf{R}_v) = -\int\limits_{V_n} d\mathbf{R}'_n\, G_{ij}(\mathbf{R}_v, \mathbf{R}'_n) \times$$

$$\times X_{ji}^{(n)}(\mathbf{R}'_n)\, E_j^{(0)}(\mathbf{R}'_n), \tag{3}$$

where $G_{ij}(\mathbf{R}_v, \mathbf{R}'_n$ is electrodynamic Green's function of the medium, in which the system is embedded (e.g., the intercellular fluid), and the integration is carried out over nanoparticle's volume. On the other hand, the viral particle is also indergone the action of electric field fluctuations $E_i^{(0)}(\mathbf{R}_v)$. As a result, the dipole moment

$$P_i^{(v)}(\mathbf{R}_v) = X_{ij}^{(v)}(\mathbf{R}_v)\, E_j^{(0)}(\mathbf{R}_v), \tag{4}$$

will be induced at the virus. Here, $X_{ij}^{(v)}(\mathbf{R}_v)$ is the virus effective susceptibility. To evaluate the energy of the external (relative to the system) field of vacuum fluctuations, which can be absorbed by a virus, one can write

$$Q = -\frac{i\omega}{4}\, \frac{1}{V_v} \int\limits_{V_v} d\mathbf{R}'_v \big\{ P_i^{(v)}(\mathbf{R}'_v), [E_i^{(v)}(\mathbf{R}'_v)\,]^* -$$

$$-[P_i^{(v)}(\mathbf{R}'_v),\,]^* E_i^{(v)}(\mathbf{R}'_v) \big\}, \tag{5}$$

where the integration is carried out over viral particle's volume.

Substituting expressions (2) and (3) in formula (5) and carrying out the statistical averaging, we obtain

$$Q = \int\limits_{-\infty}^{\infty} \frac{d\omega}{2\pi} \frac{\hbar \Omega_{kl}^{(v)}(\mathbf{R}_v)}{1 - \exp(-\hbar\omega/kT)} \big\langle E_k^{(0)}(\mathbf{R}_n)\, E_l^{(0)}(\mathbf{R}_v) \big\rangle_\omega, \tag{6}$$

where

$$\Omega_{kl}^{(v)} = -\frac{i\omega}{4}\, \frac{1}{V_v} \int\limits_{V_v} d\mathbf{R}'_v \times$$

$$\times \Big\{ X_{il}^{(v)}(\mathbf{R}'_v) \Big[\int\limits_{V_n} d\mathbf{R}'_n\, G_{ij}(\mathbf{R}'_v, \mathbf{R}'_n) X_{jk}^{(n)}(\mathbf{R}'_n) \Big]^* -$$

$$- \Big[X_{il}^{(v)}(\mathbf{R}'_v) \Big]^* \int\limits_{V_n} d\mathbf{R}'_n\, G_{ij}(\mathbf{R}'_v, \mathbf{R}'_n) X_{jk}^{(n)}(\mathbf{R}'_n) \Big\}. \tag{7}$$

When writing down formula (6), we took into account that the fluctuation fields are real-valued. The fluctuation field correlator $\langle E_k^{(0)}(\mathbf{R}_n)\, E_l^{(0)}(\mathbf{R}_v) \rangle_\omega$ can be expressed in terms of Green's function $G_{ij}(\mathbf{R}_v, \mathbf{R}'_n)$ [50, 51] of the medium, where the system is located:

$$\big\langle E_i^{(0)}(\mathbf{R}_n)\, E_j^{(0)}(\mathbf{R}_v) \big\rangle_\omega =$$

$$= -\frac{\omega^2}{c^2}\,\mathrm{Im}\,G_{ij}(\mathbf{R}_v, \mathbf{R}'_n)\,\mathrm{sign}\,\omega, \tag{8}$$

Here, $\mathrm{sign}\,\omega = -1$ if $\omega < 0$, 1 if $\omega > 0$, and 0 if $\omega = 0$.

In the near-field approximation, when the retardation processes are neglected,

$$\left\langle E_i^{(0)}(\mathbf{R}_n)\, E_j^{(0)}(\mathbf{R}_v)\right\rangle_\omega = -\frac{\hbar\omega^2}{c^2}\, T_{ij}(\mathbf{R}_v - \mathbf{R}_n),$$

$$\omega \ll c/\,|\mathbf{R}_v - \mathbf{R}_n|, \tag{9}$$

where

$$T_{ij}(\mathbf{R}_v - \mathbf{R}_n) = \frac{3n_i n_j - \delta_{ij}}{|\mathbf{R}_v - \mathbf{R}_n|^3},$$

$$n = (\mathbf{R}_v - \mathbf{R}_n)/|\mathbf{R}_v - \mathbf{R}_n|. \tag{10}$$

The energy Q (see Eq. (5)) can be sufficiently high to induce a damage or destruction of molecules-receptors on the viral shell surface, which considerably reduces the pathogenicity of the virus. Evaluations of the energy Q for a viral particle about 100 nm in dimensions and a nanoparticle about 10 nm in dimensions bring us to values ranging from $0.1kT$ to several kT's. Expectedly, this energy is sufficient to deactivate the virus [52].

Let us discuss, in more details, the ways that can be used to substantially reduce the infectious activity of a virus by switching on the mechanism considered above. Here, there are two essentially different directions for the viral activity neutralization. One of them does not suggest that a viral particle penetrates into a living cell. It can be described as follows.

(a) The formation "virus–nanoparticle" is rather stable. Therefore, its geometrical characteristics can be considered different from those of the virus. Since the virus penetration through the cellular membrane strongly depends on the geometrical factor, the virus with an attached nanoparticle (nanoparticles) loses, as a rule, its capability to penetrate into the cell. Hence, its infectious activity decreases.

(b) As was indicated above, owing to the action of a local field (see Eq. (3)) on receptors on the virus surface, the molecular groups can undergo modification, up to their destruction, on receptors. Really, the tensor of effective susceptibility can acquire rather large values under resonance conditions, when its pole part becomes anomalously small. In accordance with formula (3), this results in an appreciable amplification of the local field at the viral particle. Virus receptors interact with the corresponding formations on the cellular shell following the complementary principle of the "key–lock" type. Therefore, any damage to the receptor results in that it becomes impossible for the virus to penetrate into the cell.

The other way to neutralize the virus infectious activity suggests that some viruses, even after having been treated with nanoparticles, can penetrate into the cell and infect it. This scenario is possible owing to the following reasons. First, nanoparticles may be localized not in a vicinity of all viruses that penetrated into the organism, e.g., on the mucous membrane of respiratory airway. Second, owing to the statistical origin of fluctuation interactions, a strong enough local field can be formed not in any system "virus–nanoparticle". Therefore, the virus that penetrated into the cell may start the self-reproduction process owing to the interaction of the viral DNA (RNA) with cellular organellas. If the virus penetrates into the cell without the nanoparticle, the process of viral DNA (RNA) replication is started. Newly formed viruses quit the cell through its membrane, being capable of infecting other cells. However, almost all new viruses that leave the infected cell meet nanoparticles in a sufficient number so that a reduction of their activity can occur in accordance with mechanisms (a) and (b). If the virus penetrates into a cell together with a nanoparticle (nanoparticles) localized on it, the action of the local field (of the fluctuation origin) on the system "virus–nanoparticle" may also be implemented following mechanisms (a) and (b). At last, there exists a possibility that nanoparticles block the processes of viral DNA (RNA) replication in the cell.

Hence, we may expect that the interaction between a nanoparticle and a virus should give rise to a strong reduction in the viral activity and, therefore, it can be used in clinical practice.

4. Experimental Researches of Antiviral Action of Nanoparticle Preparations

The influence of nanoparticles on viruses was experimentally studied, by using, as examples, the interaction between CeO_2 nanoparticles 2 to 3 nm in diameter or gold nanoparticles 7 to 70 nm in diameter modified by citrine (to prevent their coagulation) and herpes simplex (HSV) or influenza (H1N1) viruses. In order to determine the minimum active concentration (MAC) of preparation – a solution of CeO_2

nanoparticles 2 to 3 nm in diameter – the test-virus against HSV was introduced in a dose of 100 TCD 50/0.1 ml (the 50% tissue cytopathic dose) into a culture of RK13 cells and incubated for 1 h at a temperature of 37 °C. After the virus had been adsorbed on cells, it was removed and the cells were washed out in the nutrient medium. Then, the CeO_2 preparation was introduced into the cell maintenance medium (RPMI-1640 + 2% of fetal serum) in dilutions from 1:20 to 1:1280.

The absence of the cytopathogenic effect (CPE) of the virus, provided that it is present in the reference specimen, and the difference between the infectious titers in the experimental and reference HSV specimens allowed us to determine the MAC of preparation. The results of relevant experiments are quoted in Table 1. According to methodical guides [53], a substance or preparation is assumed to reveal the antiviral activity if the reproduction level of the virus diminishes not less than by $2 \log \mathrm{ID}_{50}$. Hence, if the concentrations of nanoparticles in the preparation are high enough (they correspond to dilutions lower than 1:80), the preparation can be considered active with respect to HSV.

Similar researches were carried out in order to determine the MAC of preparation against influenza virus A/FM/1/47 (H1N1). For this purpose, the test-virus in a dose of 100 TCD 50/0.1 ml was introduced into a culture of MDCK cells and incubated for 1 h at a temperature of 37 °C. After the virus had been adsorbed on cells, it was removed and the cells were washed out in the nutrient medium 199. Then, the CeO_2 preparation was injected into the cell maintenance medium (RPMI-1640 + 2% of fetal serum) in dilutions from 1:20 to 1:1280.

The absence of CPE with respect to influenza virus A/FM/1/47 (H1N1) in the studied cultures, provided that it does take place in the reference specimen, and the difference between the infectious titers of influenza virus larger than by $2 \log \mathrm{ID}_{50}$ allowed us to determine the MAC of preparation. Analogously to the previous case, it corresponded to a dilution of 1:80 (see Table 2).

Hence, we have demonstrated the efficient antiviral action of CeO_2 nanoparticles with respect to viruses of essentially different types, herpes simplex virus and influenza one.

As was mentioned above, the effect of a local field enhancement is one of the features that characterize the mechanism of antiviral action by nanoparticle preparations. This effect is known [54–56] to manifest itself most effectively for particles with small dimensions. We used Au preparations (the solutions of Au nanoparticles with the diameter varying from 7 to 70 nm) against influenza virus A/FM/1/47 (H1N1) in order to determine the dependence of the preparation MAC on the nanoparticle size. For this purpose, we, similarly to what was done in the previous cases, introduced the test-virus in a dose of 100 TCD 50/0.1 ml into a culture of MDCK cells and incubated it for 1 h at a temperature of 37 °C. After the virus had been adsorbed, it was removed and the cells were washed out in the nutrient medium 199. Then, the Au preparation was injected into the cell maintenance medium (RPMI-1640 + 2% of fetal serum) in dilutions from 1:20 to 1:1280. It turned out that, for small particles with the diameter less than 30 nm, the preparations demonstrated no cytopathogenic effect in the examined cultures (in this case, for particles 7–10 nm in diameter, the MAC corresponded to a dilution of 1:80 – see Table 3). The increase of the

Table 1. **MAC of CeO_2 nanoparticles with respect to the herpes simplex virus**

Concentration of CeO_2 preparation (μg/ml)	Virus titer, log ID_{50}	Inhibiting activity, log ID_{50}
1:20	2.0	4.0
1:40	4.0	2.0
1:80	4.0	2.0
1:160	5.0	1.0
1:320	5.0	1.0
1:640	5.0	1.0
1:1280	5.0	1.0
control	6.0	–

Table 2. **MAC of CeO_2 nanoparticles with respect to the influenza virus**

Concentration of CeO_2 preparation (μg/ml)	Virus titer, log ID_{50}	Inhibiting activity, log ID_{50}
1:20	2.0	4.0
1:40	2.0	4.0
1:80	2.0	4.0
1:160	6.0	0
1:320	6.0	0
1:640	6.0	0
1:1280	6.0	0
control	6.0	–

particle diameter to 20 nm resulted in an increase of MAC (the corresponding dilution equaled 1:40). The further growth of the particle size gave rise to that the preparation lost its antiviral activity.

The results of those experiments *in vitro* were verified by studying nanoparticle preparations *in vivo,* in living organisms. Namely, mices preliminarily infected with HSV were treated with the use of CeO_2 preparations in dilutions from 1:20 to 1:80. The effect became observable in a few hours after the treatment, which confirmed the high efficiency of the proposed method.

The experiments carried out by our scientific group and the analysis of the results obtained by many other scientific groups showed that a similar picture of the viral activity inhibition was also observed for various types and dimensions of nanoparticles – from metallic (Ag, Au) to dielectric (CeO_2, TiO_2) ones – and various viruses containing either DNA or RNA. Those results allow an assumption to be made that the same (universal) mechanism inhibits the viral activity in all indicated cases. In our opinion, this role can by played by the mechanism proposed in section 3.

5. Interaction between Viruses and a Nanostructured Surface, with a Surface Plasmon-Polariton Propagating along It

The technique of antiviral therapy considered above, which is based on the effect of the local field enhancement occurring at the interaction between a virus and a nanoparticle, has a substantial shortcoming. The latter is associated with the incompleteness of our knowledge concerning the action of nanoparticles on a living organism [57]. Moreover, owing to large dimensions of nanoparticles (in comparison with those for the majority of organic molecules), the problem of removing nanoparticles from the organism acquires a large importance. This means that the technique proposed above can be used only for the treatment of skin diseases, or an additional purification of organism from nanoparticles is required. Moreover, the development of a technique for purifying biological fluids from nano-objects, such as viruses, is a challenging task from the viewpoint of the independent method of antiviral therapy as well. In this section, we discuss a possibility of the elaboration of such a technique. The method is based on the effect of the interaction between nanoparticles and a nanostructured surface,

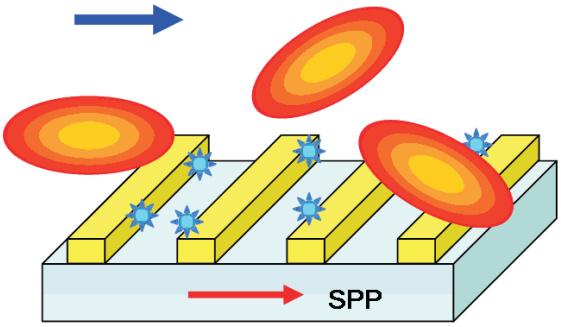

Fig. 2. Schematic setup of experiment on the interaction between viruses and a nanostructured surface

with a surface plasmon-polariton propagating along the latter [58].

Consider a nanostructured surface consisting of nanostrips on a plane metal surface. Let the linear dimensions of nanostrips amount to 10 nm and the distance between them to 100 nm. Hence, if a surface plasmon-polariton propagates under this surface, the latter plays the role of a quasi-one-dimensional photonic crystal. The previous researches testified that the local field near the edges of nanostrips can reach rather high values [59, 60]. Suppose that a biological fluid – e.g., blood consisting of rather large (of the order of several microns) organellas and dissolved nanoparticles (viruses, the dimensions of which are smaller than the structure period, or nanoparticles used for antiviral therapy) – flows over this surface. Then, owing to their small dimensions, the nano-objects will effectively interact with those sur-

Table 3. **MAC of gold nanoparticles with various sizes with respect to the influenza virus H1N1**

Concentration of Au preparation (μg/ml)	Virus titer, log ID_{50}	Inhibiting activity, log ID_{50}
nanoparticles 7–10 nm in diameter		
1:20	2.0	4.0
1:40	4.0	4.0
1:80	4.0	4.0
1:160	5.0	1.0
nanoparticles about 20 nm in diameter		
1:20	2.0	2.0
1:40	4.0	2.0
1:80	4.0	–
control	6.0	–

face regions (their dimensions are of the order of those of surface nanostructures) which are characterized by high local field values, i.e. the nano-objects will adsorbed on them (see Fig. 2).

At the same time, large organellas–they interact much weaker with the surface–can be washed off by the fluid flow. As was shown in work [61], the electrodynamic properties of a nanostructured surface with a regular arrangement of nanostrips can be described with the use of Green's function

$$I_{lk}(\mathbf{k}, z, z', \omega) = L_{lj}(\mathbf{k}, \mathbf{k} \pm \mathbf{G}, z, \omega) \times$$

$$\times G^{(0)}_{jk}(\mathbf{k}, d, z', \omega), \tag{11}$$

where $G^{(0)}_{jk}(\mathbf{k}, d, z', \omega)$ is electrodynamic Green's function of the upper medium (biological fluid), and $L_{lj}(\mathbf{k}, \mathbf{k} \pm \mathbf{G}, z, \omega)$ is the local field factor [49]. The latter, in the approximation of two Bragg planes, has the following general form:

$$L_{lj}(\mathbf{k}, \mathbf{k} \pm \mathbf{G}, z, \omega) = \Omega^{-1}_{lj}(\mathbf{k}, \mathbf{k} \pm \mathbf{G}, z, \omega), \tag{12}$$

where $\mathbf{G}$ is the smallest vector of the reciprocal lattice in the one-dimensional photonic crystal. The tensor $\Omega_{lj}(\mathbf{k}, \mathbf{k} \pm \mathbf{G}, z, \omega)$ can be easily calculated. Its components are expressed in terms of the effective susceptibility of a single nanostrip on the surface. This quantity is described with the help of electrodynamic Green's function $G_{ij}(\mathbf{k}, z, z', \omega)$. Since Green's function $G_{ij}(\mathbf{k}, z, z', \omega)$ describes the electrodynamic properties of the substrate without nanostrips, the estimations can be carried out with the use of Green's function for two half-spaces separated by a plane interface [62, 63].

Suppose now that the surface adsorbs a nanoparticle, the dimensions of which are comparable with or smaller than the period of regular structure on the surface. As was shown in works [50, 51], if a quasi-point particle is adsorbed, the interaction potential (its attractive part) between the particle and the surface is determined in terms of the effective susceptibility, $\chi^{(p)}_{ij}(\omega)$, and electrodynamic Green's function of the surface, $I_{ji}(\mathbf{k}, l, l, \omega)$, as follows:

$$U(l) = -\frac{\hbar}{4\pi^2} \int\limits_0^\infty \mathrm{Im}\Big[\chi^{(p)}_{ij}(\omega) \times$$

$$\times \int I_{ji}(\mathbf{k}, l, l, \omega)\, d\mathbf{k}\Big] \coth \frac{\hbar\omega}{2kT}\, d\omega. \tag{13}$$

Here, l stands for the distance between the nanoparticle and the surface. In particular, formula (13) demonstrates that the larger the quantity $\mathrm{Im}\left[\chi^{(p)}_{ij}(\omega) \int I_{ji}(\mathbf{k}, l, l, \omega)\, d\mathbf{k}\right]$, the larger is the potential. Green's function $I_{ji}(\mathbf{k}, l, l, \omega)$ includes the inverse matrix $\Omega^{-1}_{lj}(\mathbf{k}, \mathbf{k} \pm \mathbf{G}, z, \omega)$ (see formula (12)); therefore, its denominator looks like the determinant of this matrix. On the other hand, it is known [64] that putting the real part of singular Green's function component to zero defines the dispersion law for the surface plasmon-polariton in the nanostructured substrate,

$$\mathrm{Re}[\det \Omega_{ji}(\mathbf{k}, \mathbf{k} + \mathbf{G}, z, \omega)] = 0. \tag{14}$$

In other words, the adsorption potential (13) is maximal in the case where a surface plasmon-polariton is excited in the substrate. In addition, the evanescent field of a surface plasmon-polariton is strongly non-uniform, with its large values being observed near the edges of nanostrips. This means that one may assume that nanoparticles, the dimensions of which are comparable with the size of domains where the local field of a surface plasmon-polariton is high, are efficiently adsorbed on the surface just in those regions. Hence, a simple analysis of formula (13) enables us to propose a new method of antiviral therapy and a method of purifying biological fluids from nanoparticles consisting in a selective adsorption of nanoparticles, the dimensions of which are smaller than the period of nanostructure on the surface and, at the same time, are comparable with the dimensions of strong evanescent field regions.

As one can see from formula (13), the interaction between a nanoparticle and the surface also depends on the effective susceptibility of the nanoparticle, $\chi^{(p)}_{ij}(\omega)$. Besides all that, the linear response of the nanoparticle to an external field is also governed by its interaction with the environment [47]. Therefore, the effective susceptibility depends on the structure of the surface, in a vicinity of which the particle is localized. This means that the geometry of nanostructures on the surface can increase the values of $\chi^{(p)}_{ij}(\omega)$, which automatically gives rise to the enhancement of the interaction between the particle and the surface. Thus, adequate models for the calculation of the effective susceptibility can not only improve our understanding of details of the interaction, but can provide specific recommendations concerning the preparation of surfaces for the effective adsorption of specific nanoparticles.

From the physical viewpoint, the determination of the effective particle susceptibility also implies that the interaction between a particle and the surface should be taken into account. Really, since the physical meaning of the effective susceptibility is reduced to the linear response of a particle to an external field [47], the quantity $\chi_{ij}^{(p)}(\omega)$ must be determined making allowance for the effects of self-action both by means of the environment and through the interaction between the particle and the surface (see Fig. 3). In the zeroth-order approximation, the effective susceptibility can be calculated by supposing that a particle interacts with the plane perfect surface. In this case, the non-uniform distribution of the local field inside the particle can be neglected. This model is widely used while calculating the scattering of surface waves by nanoparticles with the shape of an ellipsoid of revolution [65]. In the framework of this model, the calculations of the effective susceptibility of nanoparticles, $\chi_{ij}^{(p)}(\omega)$, can not only elucidate some details of interaction, but also can provide quite specific recommendations concerning the preparation of surfaces for the effective adsorption of specific nanoparticles. It is clear that the possibilities of this model with respect to the calculation of the effective susceptibility of a single nanoparticle are restricted. The model does not consider the non-uniformity of the field inside the particle and, what is the main thing, does not take a spatial structure of the substrate into account. Those restrictions can be partially eliminated by using the approach proposed in work [47], where the following expression was obtained for the effective susceptibility:

$$\chi_{ij}^{(p)}(\mathbf{R},\omega) = \\ = \chi(\omega)\left[\delta_{ji} + k_0^2 \int\limits_{V_p} I_{ji}(\mathbf{R},\mathbf{R}',\omega)\,\chi(\omega)\,d\mathbf{R}'\right]^{-1}. \quad (15)$$

Even the cursory analysis of formula (15) shows that the model proposed involves both the non-uniformity of the local field in a nanoparticle and the presence of a nanostructure on the surface. However, the calculation of the effective susceptibility in model (15) is rather a complicated procedure, which is connected, first of all, with the calculation of the integral at points, where $\mathbf{R}$ and $\mathbf{R}'$ coincide. Nevertheless, there exist regular methods for calculating such integrals [66], so that the determination of the effective susceptibility by formula (15) is possible. On the other hand, such a calculation can provide some important information on the structure of the surface which is to be prepared for specific types of nanoparticles.

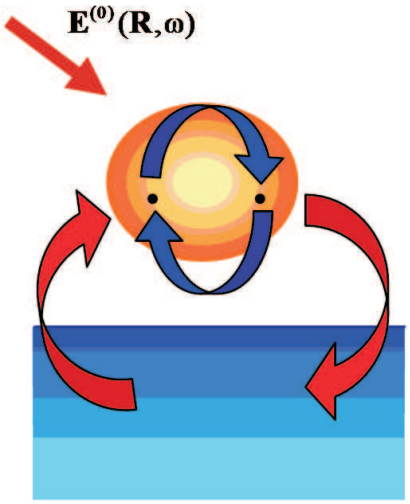

Fig. 3. Toward the determination of the effective particle susceptibility

It should be noticed that, till now, there is no satisfactory theory describing the adsorption of non-point objects onto a solid surface. This means that, for today, the application of formula (13) is a single possible way for the estimation of the binding energy between a particle and the surface and, hence, the efficiency of the method proposed in this section. However, we hope that the approach developed in work [48] to find the potential of the interaction between nonlinearly polarizable particles can also be used to construct the theory of adsorption of non-point objects on a solid surface.

Nevertheless, the method proposed for the purification of biological fluids has a substantial shortcoming. The matter is that, as is testified by numerous results obtained in the previous experiments carried out in our group, the effect of the local field enhancement in nanostructured striped structures can be strongly screened immediately near the surface. In this case, however, owing to an effect that is an analog of the Talbot effect [67] in optics, regular structures of a strong field can be formed at rather long distances from the surface where, as we saw from formulas (13) and (1), the minima of the interaction potential between nanoparticles (or mesoparticles, organellas) and the field can emerge. As a result, those particles, which should be removed from the fluid, are accumulated in the strong-field regions and remain there as far as a surface plasmon-polariton is

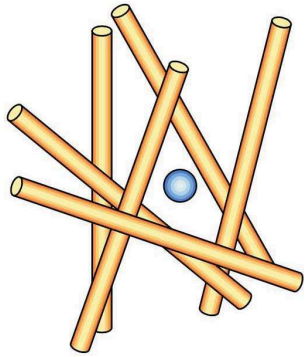

Fig. 4. Schematic setup of experiment on the interaction between a nanoparticle and a system of nanothreads

excited on the surface. In this case, we may stop the pumping of the substance through the system, switch off the laser, which excites surface plasmon-polaritons, and pour off the remnants of the liquid strongly contaminated with nanoparticles. After that, the purification cycle can be repeated as many times as needed.

6. Purification of Biological Fluids on the Basis of the Local Plasmon Resonance

In addition to the method proposed above for the purification of biological fluids (such as blood or blood plasma), which is based on the effect of the local field enhancement near nano-inhomogeneities on a metal surface, when a plasmon-polariton propagates under the latter, we propose the idea of a method for the purification of biofluids on the basis of the effect of localized plasmon resonance in nanosystems.

Consider a system consisting of nanothreads, with the average distance between them being enough for blood or plasma organellas to pass almost freely through the system, i.e. when the average distance between the threads is about a few microns (see Fig. 4). As was done in the previous case, let us write down the attractive part of the interaction potential between a nanoparticle and a separate thread in the system in the form

$$U(l) = -\frac{\hbar}{4\pi^2}\int\limits_0^\infty \mathrm{Im}\Bigg[\int\limits_{V_n} d\mathbf{R}\int\limits_{V_p} d\mathbf{R}'\times$$

$$\times X_{ij}^{(n-p)}(\mathbf{R}',\omega)\, I_{ji}(\mathbf{R},\mathbf{R}',\omega)\Bigg]\,\coth\frac{\hbar\omega}{2kT}\,d\omega, \qquad (16)$$

where $l = |R_p - R_n|$ is the distance between the nanoparticle and the nanothread, R_p is the position of the nanoparticle center, R_n is the coordinate of a point on the nanothread axis that is the nearest to the nanoparticle, and $I_{ji}(\mathbf{R},\mathbf{R}',\omega)$ is electrodynamic Green's function of the system of nanothreads (it can be calculated, e.g., in the framework of the pseudovacuum Green's function method). The integration is carried out over the nanothread, V_n, and nanoparticle, V_p, volumes. The effective susceptibility of the nanoparticle, $X_{ij}^{(n-p)}(\mathbf{R}',\omega)$, can be calculated using one of the methods discussed above. Similarly to the previous case, we may assert that, since the pole part of Green's function $I_{ji}(\mathbf{R},\mathbf{R}',\omega)$ describes plasmon resonances in the system of nanothreads (these resonances are evidently nothing else but localized plasmons), such conditions can be created (e.g., by selecting the corresponding parameters of external radiation) that this pole part can be made minimal. This means that it is possible to strengthen the interaction potential between the particle and the nanothread to a required magnitude in a controllable way. Since this interaction will be considerably larger for the nanoparticle than for a mesoparticle (in the latter case, the local fields from different threads screen one another), there emerges the idea of a controllable nanoparticle adsorption in a system of nanothreads. This controllable adsorption can also be used to purify biofluids from nanoparticles.

7. Increase of Human Interferon Synthesis Efficiency by Nanoparticle Preparations

The penetration of alien agents such as, e.g., viruses or cancer proteins, into cells of the majority of vertebrate organisms is known to be accompanied by a secretion of a special protein, interferon. Owing to the presence of the latter in the organism, its cells become resistant against those agents. Hence, the generation of interferon by the cells in the presence of hostile agents can be regarded as a response similar to the reaction to vaccination.

There are a lot of methods to fabricate interferons in modern pharmaceutics (see, e.g., works [68–71]). One of the methods to obtain human leukocytic interferon consists in that the virus-inductor is prepared by cultivating the strain H of Newcastle disease virus (NDV) in 9- to 10-day-old chicken embryos. The infecting virus dose equal to 104 TCD 50/ml (a cytoplasmic virus dose that induces the damage or destruction of 50% of infected culture) was injected into the allantoic cavity of embryo with the help of a syringe and under sterile conditions. Then, the em-

Table 4. **Interferon titers at the addition of NDV and CeO_2 nanoparticles**

No.	Preparations	Interferon titer, IU/ml					
		Experimental series					
		1	2	3	4	5	6
1	Interferon level in the initial leukocyte suspension	100	100	0	0	100	0
2	Interferon level after only CeO_2 suspension was added	100	100	0	0	100	0
3	Interferon level after only NDV suspension was added	800	800	800	1600	1600	400
4	CeO_2 nanoparticles were introduced simultaneously with the NDV	1600	1600	1600	3200	3200	800
5	CeO_2 nanoparticles were introduced 2 h after the NDV	1600	3200	6400	12800	12800	800
6	CeO_2 nanoparticles were introduced 4 h after the NDV	3200	6400	6400	12800	12800	1600

bryos were incubated for 48 h at a temperature of 37.5 °C. After incubation, the embryos were cooled down to a temperature of 4 °C. The allantoic fluid was pumped out from them and used as a viral inductor of interferon. Leukocytes were suspended in the nutrient medium at a temperature of 37.5°. Then, the viral inductor was added and the culture was incubated at a temperature of 30.5 °C. Afterward, the viral inductor was separated, the nutrient medium was added to the precipitate of leukocytes, and the suspension was maintained for 18–20 h at 37.5 °C. The interferon synthesized using this procedure and accumulated in the nutrient medium had an antiviral activity of 800–1000 international units (IU) per 1 ml of preparation.

This procedure of interferon fabrication can be considerably improved by using the allantoic NDV (previously purified and concentrated with the help of its ultrafiltration through membranes with the pores 0.1–0.45 mm in diameter) for induction. The antiviral activity of the interferon obtained in such a way amounted to 8000–10000 IU/ml.

Those methods for fabricating interferon are evidently rather complicated technologically. Moreover, a reduction of the cytoplasmic action of viral inductor and the increase of interferon yield are achieved through rather a complicated and expensive sequence of technological operations.

One should bear in mind that nanoparticles and viruses, owing to their interaction with one another by means of vacuum field fluctuations, can form resistant systems so that the infectious activity of viruses can be strongly inhibited. On this basis, a new method of interferon synthesis can be proposed. Namely, this method, which would be characterized by an increased yield of interferon, a simplified procedure, and a reduced cytopathic action of viral inductor after the production of interferon having been started, could be composed of the following technological stages: (i) human leukocytes are separated, and their suspension in a nutrient medium is prepared; (ii) the Newcastle disease is induced with the use of allantoic virus; (iii) the viral inductor is inactivated; and (iv) in about 2 to 4 h after the solution of allantoic virus of Newcastle disease has been introduced into the suspension of leukocytes, nanoparticles of a substance (selected from those substances that have the minimum toxic influence on the living organism cells) are added. It turned out that this procedure allows interferon with a stable value of antiviral activity titer of 11000–14000 IU/ml to be obtained and the death fraction for the cells producing interferon to be diminished to 25%.

Experimentally this technique was testified by determining the capability of cerium dioxide nanoparticles to affect the interferon production *in vitro*, in a culture of peripheral donor's blood. In particular, the reference interferon inductor (NDV) was added to 3 million blood leukocytes and incubated for 24 h at 37 °C. In other words, the biosynthesis of interferon took place simultaneously with the induction and without changing the nutrient medium. In 24 h, the supernatant fluid was gathered, its pH was changed to 2.0, and the fluid was held for 48 h at 4 °C. Then the fluid pH was restored to 7.2, and the interferon level was determined following the standard method that uses the inhibition of cytopathogenic actions of virus-indicator (the virus of vesicular stomatitis, strain Indiana) in the transferred culture M19 or L41, in the culture medium RPMI-1640 with 10% of fetal serum (Sigma), as was described in work [72]. For this purpose, the cell culture was treated by corresponding dilutions of the interferon-containing fluid in 96-well trays (Costar, USA). After 18 h of the incubation at a

temperature of 37 °C in the presence of 5% CO_2, the culture fluid was removed, the cells were washed out once in Hank's solution and infected with the virus of vesicular stomatitis (strain Indiana, BBC) with a multiplicity of infection 100 CPD 50/ml. After the incubation at 37 °C, the cells were washed out in Hank's solution, and a fresh nutrient medium was added. The results were determined in 24–48 h, when a complete cell degeneration took place in the reference research with the introduced NDV, provided that the monolayer of culture cells in the reference wells did not change. As an interferon titer, we considered the reciprocal of the preparation dilution, at which the cell culture was completely protected from the pathogenic action of indicator virus in 50% of wells.

While studying the influence of nanocrystalline cerium dioxide, CeO_2 nanoparticles 2 to 3 nm in dimensions and with an initial concentration of 0.1 mol/l were used. Here, it should be noted that the conditions for the experiment with the CeO_2 nanoparticle application were as follows: in the first group, the CeO_2 nanoparticles were introduced simultaneously with the NDV; in the second group, the CeO_2 nanoparticles were introduced in 2 and 4 h after the introduction of inductor-virus (NDV). Six series of experiments were carried out. The results obtained are quoted in Table 4.

From Table 4, one can see that, if the suspension of nanoparticles is added in 2 or 4 h after the infection of a leukocyte suspension with the Newcastle disease virus, the maximum titer of interferon reaches 12800 IU/ml, which is 8 times larger than that in the reference research (1600 IU/ml), where nanoparticles were not added, and 4 times larger than in the case of the addition of the suspension of nanoparticles simultaneously with the leukocyte infection with NDV (3200 IU/ml). An interferon level of 800–1600 IU/ml after addition of only the NDV suspension corresponded to that obtained in the standard way [68]. The introduction of CeO_2 nanoparticles simultaneously with NDV doubles the interferon yield, whereas the introduction of nanoparticles in 2 or 4 h after the introduction of NDV gives rise to the interferon yield that is 4 or 8 times higher than that obtained in the standard way.

Thus, our experiments confirmed the idea to increase the efficiency of interferon production by using the suspension of nanoparticles: the virus suspension is added firstly to the suspension of leukocytes; and the suspension of nanoparticles is introduced with a delay of 2 to 4 h.

8. Conclusions

In this brief review, we intended to acquaint the wide scientific community of Ukraine with works dealing with the implementation of ideas in antiviral therapy and the corresponding activity in the domain of physics of nanosystems that is carried out at the V.E. Lashkaryov Institute of Semiconductor Physics of the National Academy of Sciences of Ukraine (Kyiv), the D.K. Zabolotnyi Institute of Microbiology and Virology of the NAS of Ukraine (Kyiv), and the Institute of High Technologies of the Taras Shevchenko National University of Kyiv [49, 53, 59, 77]. The main idea of this activity consists in the application of the local field enhancement effect, which is inherent only in nano-objects and can manifest itself in the system nanoparticle–virus. The authors proposed, for the first time, a mechanism for the description of the influence of nanoparticles on viruses. This mechanism is based on the action of the field of vacuum fluctuations that are immanent to any physical system, rather than the action of external radiation directed onto the system. The proposed mechanism is universal. It does not depend on the details of nanoparticle and virus structures, which is confirmed by numerous experiments for viruses of various origins and structures carried out both by the authors of this work and in other scientific groups (see, e.g., works [29, 30]). The proposed idea was also developed to be applied to either a nanostructured surface, along which a surface plasmon-polariton propagates, or a system of nanothreads in the state of local plasmon excitation in order to purify biological fluids from viruses and nanoparticles. In addition, it was found out that the treatment of a suspension of leukocytes by the nanoparticle-containing one (the viral suspension and the nanoparticle one should be sequentially added to the leukocyte suspension with a delay of 2 to 4 h) considerably increases the efficiency of the interferon production by cells.

It should also be noticed that the systems that were considered in this work are colloid solutions. It is known [73, 74] that the ζ-potential in such systems is increased. The typical dimensions of ζ-potential localization near the surface of nanoparticles are confined by the Debye screening length and amount to about 1 nm. At the same time, the characteristic dimensions of particles in the system examined in this work are of the order of 10–100 nm. This means that the influence of the ζ-potential on the electrodynamic properties of the system is small. In general, this influence is reduced to the emergence of a shell around

a nanoparticle, which is formed by the double layer of ions near the particle surface. This means that, for the influence of the ζ-potential to be taken into account, the particle should be considered as if it has a shell. The presence of shells around the particles can result, in particular, in a variation of the effective susceptibility. In other words, the effective susceptibility of particles has to be calculated with regard for a thin shell around them [75, 76].

The authors express their sincere gratitude to the colleagues and collaborators who took part at various stages of this work and the preparation of the paper: N. Zholobak, V. P'yatnytsya, O. Radchenko, L. Rybalko, V. Sterligov, and O. Shcherbakov.

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Received 05.11.12.
Translated from Ukrainian by O.I. Voitenko

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НАНОФІЗИКА ТА АНТИВІРУСНА ТЕРАПІЯ

Р е з ю м е

Запропоновано новий механізм взаємодії вірусів з наночастинками, що ґрунтується на притаманному тільки нанооб'єктам ефекті підсилення локального поля, який може проявлятись у системі наночастинка–вірус. Основною ідеєю запропонованого механізму є розгляд дії завжди притаманного будь-якій фізичній системі поля вакуумних флуктуацій. Цей механізм є універсальним. Він не залежить від деталей структури наночастинки та вірусу, що підтверджують численні експерименти, проведені як авторами роботи, так і іншими науковими групами. Обговорено також новий метод очищення біорідин від нанооб'єктів – наночастинок та вірусів. Метод ґрунтується на вибірковій взаємодії нанооб'єктів з наноструктурованою поверхнею, вздовж якої поширюється поверхневий плазмон-поляритон, або з системою нанониток, що знаходяться в умовах збудження на них локального плазмон-поляритона. На основі запропонованого методу послаблення вірусної активності під дією суспензії наночастинок, розроблено і експериментально перевірено новий ефективний спосіб отримання людського лейкоцитарного інтерферону.