The use of the channelforming of polyene antibiotics at the muscle performance

V.Kh.Gasimova
Baku State University

Abstract: This study intended to compare the action of levorin A_2 antibiotic on permeability properties bilayer lipid membranes and biological muscle membranes to ions and some organic molecules. The molecular organization of levorin A_2 complexes responsible for the induced ion permeability in lipid and biological membranes remains obscure. Comparison of the results in lipid bilayers and muscle membranes can be used the polyene action to amplify the muscle performance. It's showed that nonaromatic and aromatic heptaene polyene macrolide antibiotics induced in lipid bilayers and frog isolated skeletal muscle fibers cation conductance for K^+, Na^+, Ca^{++} ions, and neutral molecules in the following number series: H_2O > urea > acetamide > glycerine > ribose > arabinose > glucose > saccharose. In the presence of levorin A_2 can be the speed of motion in tissue of muscle fibers of energy-dependent substrates and escaping them of the derivated products of metabolism at intensive muscle performance.

Keywords: membrane, system, ions, molecular organization**.**

One of the basic problems of cell biology is the creation of new transport systems in cell membranes which is capable selectivity to transfer in the cells ions and energy-dependent substrates. It's known the channels of muscle cell membranes selective permeability to Na +, K +, Ca ++ ions and also various substrates, in particularly monosaccurose for maintenance of process of a glycolysis and oxidative phosphorylation with the purpose produce of chemical energy such as ATF and creatine phosphate. It is established, that at muscle performance the ion permeability muscle cell membranes increases at 5-10 of times as a contrast to rest state and the move of K^+ ions from muscle cells is accelerated and some substrates from cells pass to extracellular phase. At muscle performance the process of absorption of a glucose by skeletal muscles and the activity of membrane enzymes is increased. It becomes clear, that in the period of intensive muscle performance the need of an organism to ions, carbohydrates and other organic substrates are increased and the channels of muscle cells start to working with high intensivity. However the activity of native channels is limited and, therefore they don't have capacity in unit of time to deliver in muscle cells organic compounds in indispensable quantity. The power of muscle performance step-by-step weakens and fast there comes the fatigue. Here there is a necessity in activation of native cell channels by the help of exogenic compounds which is capable to form into the muscle membranes cation-selectivity of channels. Levorin A_2 have been shown to mediate changes in permeability by forming ion-selective structure channels in thin lipid membranes.

The effects of the membrane-active channelformers pharmaceutical of polyene antibiotics (PA) on training loads and muscle performance of sportsmen were investigated. The dependence of polyene-induced cation and carbohydrates on antibiotic different structure in muscle membrane was studed. The biological effect of PA is the formation in the membranes of structural ion channels which permeable for ions and organic substrates. The PA have high affinity to biological membranes, which there are sterols of definite structure. On some models experimental animals (rats, rabbits) was showed, that the use of PA leads to decreasing of a level of cholesterol in a blood on the average on 50 mg %. The experiments at the action some of PA clearly demonstrated the increase a movement of blood in the vessels for a unit of time. It is established, that the intravenous introducing of sodium salt of levorin in a dose 4 000 - 6 000 units / kg body produces the increase coronary blood of movement on the average 19 ± 2 % - 33 ± 4 %. It is supposed, that the use of PA in a complex with dimethyl sulphoxside will to increase of PA selectivity action on the pathogenic microorganisms. Reduced above effects of PA were interpreted as render beneficial influence on functionability of the sportsmen, and on rehabilitation processes.

It is known, that the training of the sportsmen is accompanied by limiting physical and psycho-emotional of loadings and demand from human's organism a new accommodate of levels. Therefore perfecting only techniques of training occupations is turning out insufficiently for dilating physical potentialities of the person. For achievement of sporting outcome the sportsmen and the coaches search for unconventional means of training and so in a modern world is observing the pharmacological boom-namely is watched, the usage of medicinal preparations for increase of physical efficiency and fast recovery of action of main system in organism (12). At the same time, tactics the usage of the drugs with comprehension of finest mechanisms of their action and functioning of leading systems of an organism in conditions of the tight muscle performance is indispensable. Both during an exercise stress of the sportsmen, and after leading recovery there should be a legible representation about the molecular mechanism of action of an assigned pharmacological drug. At the using of pharmacological drugs for increasing of physical efficiency of the sportsmen it is necessary also to have legible representations about main specifications of a functional condition of an organism, and also current power costs in a period of trainings and competitions.

In the present time there is a definite, though also conditional, the classification in a system of pharmacological maintenance of muscle performance a group of drugs, which is using in a conditioning cycle of the sportsmen. The section which one, outgoing from nature of drug action, is possible to separate on some groups:

1. The drugs of plastic and power action (antihypoxsants), satisfying heightened requirements of an organism basically ingredients in conditions of the tight muscle performance (vitamins, ATF, organic salts, inozinum, riboxinum, methyluracilum, amino

acids, non-saturated fatty acids etc.).The antihypoxsants there are plastic and power regulators of the exchange, disturbed by a hypoxia. Here, also, it is possible should be refer a drugs defiant of protein metabolism – steroid and nonsteroid anabolics (11,17);

2. The drugs contributing to maximum functioning of the main organs of detoxification (a system of urination, gastrointestinal channel) and accelerating processes after leading of recovery at the expense of linkage and ascent of metabolites (sorbents, alkalines) by improvement renal and cerebral moving of blood (nootrops-aminolon, pyracetamum, cerebrolysinum, pyriditolum etc.) (3,11).

3. The drugs contributing to decreasing of formation of toxic metabolites in during tight muscle performance and lowering damaging action last: antioxidants, the stimulators produce of blood, liverprotector, to which one should be refer α -tocopherol, ubixinon, haemostimulinum, kobalamid, allocholum etc. (11,12).

4. The drugs contributing to strengthening of immunity at tight muscle performance conditions-curantylum, methyluracilum, dalargin, polidan etc. (9).

All groups of pharmacological compounds are various on the mechanism of action. Unfortunately till now there is no legible classification of their professional orientation, i.e. direct connection with training process. In particular, the mentioned above classification of pharmacological agents, does not allow to answer a lot of problems: what drug or group of drugs is expedient for using on a background different on nature of training loads, on what (expedited or set aside) effect of training we attempt to affect, whether by possible the decrease of efficiency of a training cycle at enough long-lived application of a definite drug and what should be thus tactics of the coach and doctor (12).

Recently in clinical medicine the fissile attempts are undertaken to systematize a plenty of pharmacological drugs on their final effect, irrespective of diversiform the mechanism of action. However, to use drugs with the different a mechanism of their action is very problematic. The many-sided nature of pathogenetic links of development hypoksiya of a syndrome, arising in an organism at a deficit of oxygen at intensive muscle performance, demands the conforming pharmacological correction (11). It basically is connected to attempts of the explorers to find high-performance against sciatica of a means among drugs of different pharmacological groups known in clinical practice, and synthesis of the drug molecules and their derivatives with established chemical structure.

It is known, that the cellular membranes are the primary target of action of pharmacological drugs and the efficiency of their interaction with membranes depends on the chemical structure is using drug. Allowing it, we attempted to approach to the solution of the given problem completely from a stand of looking up of pharmacological drugs with the known molecular mechanism of their action having high affinity to biological membranes, and also biological effects, having to a large spectrum of action. The speech goes about drugs having the unconventional mechanism of action, in conditions of the tight muscle performance in combination with nutrient ration of the sportsman. There is the alone one class natural membrane-active compounds - polyene

antibiotics (PA) such drugs, which one can be used for the solution of many problems and, in particular, concerns to a bioenergetics of muscle performance (7). The main representatives of PA are amphotericin B, nystatin, mycoheptin, levorin and their derivatives, chemically modified in different side of the molecule. The general in chemical structure of PA there is a lactonic rings keeping a hydrophobic chain with definite number of double bonds and a hydrophylic chain is keeping hydroxyl and carbonyl groups (7,29). The polyene antibiotics are the favourite instruments in hands of the explorers for analysis of the molecular mechanism of the transport of ions through lipid and cell membranes (7,22,24). In the basic of biological effect of PA having the formation by them in lipide membranes in a complex with cholesterol and other sterols of structural ion channels of molecular size (31).

The polyene channel represents dynamic structure consisting of several moleculas of antibiotics and a sterol. Inside pore of a channel is covering by hydrophylic groups, but hydrophobic side of the PA is connected to a sterol molecules (7). The polyene antibiotics increased the conductance of bimolecular lipid and cell membranes for univalent anions and cations by the mechanism of formation of ionic channels (7). The membrane activity and selectivity of action of PA depends on the structure of antibiotics molecule, and on the structure of a sterol molecule (7). The availability of PA molecules to chemical modification at the functional groups opens an actual capability of obtaining new derivatives of PA with a new physico-chemical properties [19,31,34]. So, for example, within the framework of the all-European scientific program “Human gene therapy”with the help positively of charged of PA molecule has appeared possible to create a system of carry of oligonucleotides and conforming genes through lipid membranes and to amplifier transport oligonucleotides in a genome of mammals cells [27,28]. The investigation conducted in our lab, and also the data of the foreign workers give the basis to suppose, that the greatest concern is introduced by the modification hydrophilic and hydrophobic chain of PA molecule.Only this kind modification in polyene molecules are responsible for a biological activity and selective permeability of the membranes for ions and organic compounds [7,19,24,27,28,34].

The assurance of that PA can be effectively should be using in during sporting activity is grounded, at first, on knowledge of the molecular mechanism of action of PA and, secondly on polyfunctionality of their biological effect [7,21].

The polyene antibiotics have high affinity to biological membranes, which there are sterols of definite structure [22, 29,]. On some models experimental animal (rats, rabbits) was showed, that the use of PA leads to decreasing of a level of cholesterol in a blood on the average on 50 mg % [14]. PA also reduce parameters reaction sedimentation of erytrocites and concentration of a sialine acid, which one is prosthetic group of glycoproteins (γ-globulin) [14]. At interaction of PA with water they, approximately, in 2-3 times reduce surface tension of aqueous solutions, that promotes increase of flowability of a blood and acceleration of motion on blood vessels in the rest, and at

muscle performance [10] PA, being channel-forming compounds, can induce in cellular membranes of muscle fibres the formation of additional channels of a permeability and speed up a going into of the cells and tissue of muscle fibres of indispensable energy-dependent substratums and to speed up the exit of the produced products of a metabolism at intensive muscle performance. As the main reason for the so optimistical supposition it is the data obtained in a series of model experiments on animal. At research action of some PA, in particular Na-salts of levorin, on a blood supply of heart for some animal were obtained interesting results. So, in experience on grapnels the coronary blood stream (by quantity of a blood, flowing off from a coronary sine, for a unit of time) was loged, quantity of oxygen, consumed by heart, and tone of coronal vessels [10]. It is established, that the intravenous introducing of sodium salt of levorin in a dose 4 000 - 6 000 units / kg body produces accordingly increase coronary blood of movement on the average on 19 ± 2 % and 33 ± 4 %. Thus the tone of coronal vessels increases on 20 % and 32 % as contrasted to initial [10]. Thus, the above-stated experiments visually demonstrate increase of a volume of a movement of blood on vessels for a unit of time. Under the action of PA in the membranes of muscle fibres Na + / K + -ATF-aza is activated also [30] and the amplification of the immune status of an organism take place [21]. The nutrition is a key link in maintenance of power engineering of muscle performance of the sportsmen. It is based on a principle of a balanced mode of a nutrient ration of the sportsmen. From a composition of organic compounds amounting diurnal diet of the sportsmen, the large part is necessary on carbohydrates. If in a customary mode of a nutrient, the lobe of carbohydrates makes 50 %, in the period of a muscular exercise on a lobe of carbohydrates already it is necessary about 70 % of all nutrient ration of the sportsmen. With strengthening of an exercise loads the lobe of carbohydrates is even more augmented proportionally to increasing of an exercise loads. It is known, that the organic compounds are entering with nutrition into the organism to hydrolytic decomposition under the action of the conforming enzymes is undergoing, where the carbohydrates, lipids and proteins is disintegrated up to free monosaccharides, fatty acids and amino acids. In the free form these components are entering in a thin intestine and then through walls of a thin intestine are absorptied in a blood. It is necessary to mark, that the absorption of nutrient compounds in a blood be going on through specialized structures - channels, which one are in membranes of walls of an epithelial layer. The membrane channels of muscle cells are capable to transport ions of potassium, natrium, calcium, and also definite substrates, in particular, monosaccharides for supportive the process of a glycolysis and oxidation phosphorylation with the purpose of synthesis by rich chemical energy makroergic compounds, such as ATF, creatine phosphate etc. In the period of an intensive muscle exercise the necessity for organic substrates increases and also channels start to work with the greater intensity. However specific activity of native channels is limited and, therefore they have no capacity to deliver to muscle cells of organic compounds in indispensable quantity. The power engineering of muscle

performance step-by-step weakens and fast there comes the period of tired. Here there is a necessity for activating of native cell channels and it can be made by help of exogenic drugs, which one are capable to form in membranes of muscle cells a structural ion channels with the greater conductance. To such channel-forming substunces concern of polyene antibiotics, for many of which the chemical structure is established. Make allowances for that many membrane processes - ion permeability, transport of organic compounds, oxidative phosphorylation, adhesion, action potential are well replicated on bilayer lipid membranes (BLMÌ) we, in quality the test of a system, have used BLM. By incorporation in a lipid membranes of amphotericin B and levorin it was possible to simulate process of ionic permeability for such ions as potassium, natrium, calcium, and also transmembrane transport of carbohydrates and other low-molecular weight compounds. It was showed, that amphotericin B and levorin induce in lipid membranes ion permeability, and also permeability for monosaccharides and other neutral moleculas in a following of a permeability: water > urea > asetamide > gliserin > ribose > arabinose > glucose > saccharose. It is clear, that in the period of a muscle exercise the necessity in a membrane-active compounds sharply increases. Under the action of channel-forming compounds, for example, polyene antibiotics, are possible to speed up the transport process in a muscle fibres cells of energy-dependent substrates and to actuate their synthesis at physical activity. Thus, the use of PA and their derivatives with established chemical structure will create an indispensable condition for strengthening of synthesis of energy-dependent substrates in muscle cells and the increasing of value of their membrane potential and, as a consequent, maintenance of an energy potential of an organism on more high level.

At the same time, the action of pharmacological drugs on an organism can be not effective at availability for the sportsmen of morbid conditions. This pathology can be connected with zymotic processes, which are flowing past in an organism of the sportsmen - fungi, purulent, or virus infection contaminations. The availability for the sportsmen with what or from these infection contaminations has an effect for functionability of the sportsmen, as in preparatory, so in the competitive period of time. In this connection the special attention is attracted to antibiotics of polyene structure, which one have capacity to stoped a devilopment of the pathogenic microorganisms and completely to stop them [7,20]. Here it is necessary to mark, that PA widely be used in clinical medicine for treatment various of diseases [7,21]. The biological activity of PA and selectivity of their effect on the pathogenic microorganism depend as on structure of PA molecules, on the structure of a sterol in the membranes, which is as receptor of PA, and from selection of a solvent of PA [7]. It was showed the best dissolubility of PA is in solution of dimethyl sulphoxside (DMSO) [5]. We have been supposed the use of PA in a complex with DMSO will to increase of efficiency of PA action (achievement of maximum medical effect at minimum concentrations of antibiotics), increase of the absorbtion degree and selectivity effect on the pathogenic microorganism. The selectivity

of action of PA is conditioned different sterol composition of fungi and human cells. The membranes of fungi cells are contained ergosterol, and in membranes of human cells - cholesterol [7,21]. The cells of a pathogenic fungi keeping ergosterol, in 10-100 times are more responsive to the action of PA, than human cells keeping cholesterol [7,21,24]. For PA there is a problem of the fast ascent of an antibiotic from an organism, in view of their relative toxicity at high concentrations. So, for example, some PA, including of amphotericin B, are urea toxicity [35] and hemolytic activity [32].

The relevant parameter determining toxicity of an antibiotic, is the dwell-time of an antibiotic in a membrane [7,21]. By using of PA derivatives, are possible sharply to reduce a dwell-time of an antibiotic in a membrane and by that to reduce a degree of his toxicity [6]. The majority of PA is insoluble in water. The dissolubility of PA in water is sharply increased at the joint introducing DMSO-PA in an organism. Because of that the dielectrical constant of DMSO is between water and oil (ε= 48,9) [38], there is decreasing a coefficient distribution of PA between a membrane and water and by that the toxic action of PA is sharply reduced. The water soluble a form of PA in 10 times are less effective, than at the introducing in aqueous phase of a complex ÏPA, dissolved in DMSO [11]. Moreover, the biological activity of PA in non-aqueous solutions (in pure solutions of DMSO) is completely lost [5]. The researches have shown, that the introducing a mixture of DMSO-PA in a water phase is result in formation of the self-aggregated associates of PA in aqueous solutions and only in such form PA have high membrane activity [23,25,26,33]. The frequency of formation and size of the aggregated associates of moleculas of PA increases with increase of concentration of PA in DMSO [26]. Such relevant properties as amphiphility, polarity high resorbtion and fast penetration into tissues and cells there are in a DMSO molecule [39]. The plotting 1 gr of DMSO on the skin surface after during definite time periods he found out in biological liquids in a μgr/ml: in serum after 1 hour - 4,5±2,6, after 5 hours - 5,9±2,2, after 24 hours - 1,8±0,6; in a saliva after 1 hour - 17,2±7,9, after 5 hours - 5,2±1,7, after 24 hours - 1,9±0,5; in a urine after 1 hour - 9,9±1,3, after 5 hours - 11,29±3,4, after 24 hours - 6,3±2,7 [16].

Dimethyl sulphoxside widely used for the solution of many problems in clinical medicine and cell biology [37,38]. The results of clinical tests have showed, that DMSO has ability to remove from gall channels the gallstones, and the intravenous introducing DMSO may be of benefit in the treatment of amyloidosis, uretrite, cystite and is effective in reversing intracranial hypertension [37-39]. The researches is showed, that DMSO has large therapeutic capabilities. So, for example, DMSO inhibits an aggregate of erythrocytes, improves processes of microcirculation, normalizes process of fibrinogenous, supresses xemotaksis of neutrophiles, acts on stability of a lipide matrix of cellular membranes, promotes increase of efficiency of flow of catalase reaction in conditions of a stimulation of formation of active forms of oxygen at an oxidative stress, positive influences the action on the lymphamicrocirculation and participates in recovery of the functions of lymphatic microvessels, disturbed by a staphylococcal toxin

[1,4,16,36,40]. DMSO has one more relevant property, namely, in iowl concentrations 0,01 % - 0,001 % he is capable effectively to block formation of free radicals [36]. The moleculas of DMSO, interacting with hydroxyl OH-radicals, is formed reactive of radicals-methanesulphinic acid (MSA) the following below scheme [36]:

$$H_3C - SO - CH_3 + OH\ (DMSO) \rightarrow CH_3 + H_3C - SO - OH\ (MSA)$$

In during of muscle exercise the peroxide processes considerably are activated in an organism resulting in appearance of aldehydes which one the representative by the malonic dialdehyde [2]. The peroxide oxidation of lipids (POL) is esteemed as permanently flowing past physiological process, the biological value which one of consists in renovation lipid composition of cell membranes. There is special antioxidative a system handicapping excessive development free radicals of processes in an organism, the different enzymes and low-molecular weight compounds enter in which one [2]. The activation of POL leads to change of mechanisms contributing to development of fatigue and a decrease of physical effeciency [15]. At a considerable activation in an organism of peroxide processes antioxidative system is weakly effective. In this case the prosess of free radical oxidation have damaging of action on the biological membranes, changing their permeability, disturbing function of membrane enzymes and receptors, originating in an organism different pathological processes [13].

The development a lipid peroPOL at muscle performance depends on nature of a work on hand and directivity of training exercises [7]. A capability of warning of increase of speed of free radical reaction by been using of exogenic drugs boosting power of antioxidative protection of an organism is studied [15]. The conducted researches have shown, that the exercise stress leads in a high-power zone originates processes of peroxide oxidation, increasing intensity a POL in an organism of the sportsmen, that in the total results in a decrease of physical effeciency [15]. At the muscle activity the permeability of membranes for different substrates is increased, that enhances lactatdehydrogenase activity in a blood, appearance in urine of protein and acetone, and also with an enhancement of activity antioxidante enzymes - peroxidase [15]. At physical loads for warning and the supression increasing of free radical oxidation is used exogenic thymolums from plant cells witch is rich natural antioxidants [18]. The data is showed, that capacity DMSO effectively to supress of free radical oxidation in membranes sharply increases at the introducing in their structure derivatives of PA. Allowing high speed resorbtion of DMSO in organs and tissues, it is possible to use for amplification of membrane conductance of other medicinal compounds, in particular of PA. DMSO, being by the main solvent of PA, enhances their combined biological effect sharply. It was showed, that some medicinal forms of PA have capacity to supress not only fungi, but also with the greater efficiency to affect on the purulent and virus infections [8]. Reduced above data demonstrate, that usage membrane-active channelforming of pharmacological drugs, as PA, can render beneficial influence both on functionability of the sportsmen, and on rehabilitation processes.

REFERENCES

1. Bril G.E., Zaxarova E.I., Experiment. and Clinic. Pharmacol.(in Russia), **61** (4), 54- 56 (1998).
2. Vladimirov Yu.A., Archakov A.I., Peroxide oxidation of lipids in biological membranes, Printed by Nauka, Moskou, 252 (1972).
3. T.A., S.B. Seredinin, Experiment. and Clinic. Pharmacol.(in Russia), 61 (4), 3-9 (1 998).
4. Garbuzova V.Yu., Davidov V.V., Experiment. and Clinic. Pharmacol.(in Russia), **61** (6), 62-64 (1998).
5. Kasumov Kh.M., Shishlov Yu.V., In. A Biology and technological advance", 223 - 226 (1974).
6. Kasumov Kh.M., Malafriev O.K., Studia Biophysica, 89 (1), 71-78 (1982).
7. Kasumov Kh.M. Molecular mechanism of interaction of polyene antibiotics with lipid membranes. The monography (in Russia), Baku, 1 - 224 (1 986).
8. Kasumov Kh.M., Kasumova F.G., Gaibova G.R., In book of Azerbaycan State Academy of Physical Culture and Sport, Baku, 37 - 38 (1996).
9. Kirillov V.I., Pediatriya, 9 - 12 (1998).
10. Levorinum and its clinical application. In book LN I IA, Sankt Petersburg (in Russia), 1 - 159 (1970).
11. Lukjanchuk V.D., Savchenkova L.V., Experiment. and Clinic.Pharmacol. (in Russia }, 61 (4), 72 - 79 (1 998)
12. Makarova G.A. General and individual problems of sporting medicine. Krasnodar (in Russia) 1 - 242 (1992).
13. Meerson F.Z., Pathogeny and warning stress and ischemic damages of heart. M.: medicine (in Russia}, 269 (1984).
14. Mycoheptinum and its clinical application. In book LNIIA, Sankt Petersburg-Moskou .(in Russia),. 1 - 112 (1973).
15. Mikhaylov S.S., Faktor E.A., In book" State of the art and actual problems of physiology of sports ", Sankt Petersburg, 65- 69 (1989).
16. Muravyov Yu.V., Doctor dissertation (in Russia }, Moskou, 1989.
17. Smirnov A V., Kivoruchko B.I. Anesthesiology and reanimatoiogy (in Russia), (2), 50 - 55 (1998).
18. Solodkov A.S., Zinchenko T.A., Davidenko D.N. et al., In book " State of the art and actual problems of physiology of sports ", Sankt Petersburg, 115 - 123 (1989).
19. Blanc I., Bueno Da Costa M., Bolard J., et al, Biochim. Biophys. Acta, **1464**, 299 - 308 (2000).
20. Bolard J, Future prospects with polyene antibiotics. In Bioactive Metabolites from microorganisms. Ed. M.E. Bushe and U. Grafe Elsevier, 151 (1989).
21. Brajtburg J. and Bolard J., Clinical Microbiology Reviews, **9** (4), 512-531 (1996).
22. Cotero B.V., Rebolledo-Antunez S. and Ortega-Blake I., Biochim. Biophys. Acta, **1375**, 43-57 (1998).
23. Coutinho A. and Prieto M., Biophysical Journal, **69**, 2541-2557 (1995).
24. Cybulska B., Bolard J., Seksek O., et al, Biochim. Biophys. Acta, **1240**, 167-178 (1995).
25. Gaboriau F., Cheron M., C. Petit et al, Antimicrobial Agents and Chemotherapy, Now., 2345-2351 (1997)
26. Gaboriau F., Cheron M., Leroy L. et al, Biophysical Chemistry, **66**, 1-12 (1997).
27. Garcia-Chaumont C., Seksek O., Grzybowska J., Borowski E. and Bolard J., Pharmacol Ther., **87** (2-3), 255-277 (2000).

28. Garcia-Chaumont C., Seksek O., Jolles B., et al, Antisense Nucleic Acid Drug Dev., Jun., **10** (3), 177-184 (2000).
29. Hartsel S.C., Benz S.K., Ayenew W. et al, Eur. Biophys. J., **23**, 125-132 (1994)
30. Jolles B. and Bolard J., Antisense Nucleic Acid Drug Dev., Jun., **10** (3), 177-184 (2000).
31. Kasumov Kh. M., Borisova M.P., Ermishkin L.N., et al, Biochim. Biophys. Acta, **.551**, 229 - 237 (1979).
32. Mazerski J., Cybulska B., Bolard J. et al, Drugs Exptl. Clin. Res., **12**, 627-633 (1986).
33. Mazerski J. and Borowski E., Biophysical Chemistry, **57**, 205-217 (1996).
34. Samedova A.A., Kasumov Kh. M., Eastern Medical Journal-Baku, **3** (1-2), 70-72 (1998)
35. Shell R., Tran N. and Bamhall J., Biochem. Biophys. Res. Communs., **159**, 165-170 (1989).
36. Simic M.G.. Mutat. Res., **202**, 377 - 386 (1988).
37. Swanson B.N., Rev. Clin. Basic. Pharm., **5**, 1-33 (1985).
38. Zhi-Wu Yu and Peter J. Quinn, Bioscience Reports, **14** (6), 259-281 (1994).
39. Zhi-Wu Yu and Peter J. Quinn, Molecular Membrane Biology, **15**, 59-68 (1998).
40. Zhi-Wu Yu and Peter J. Quinn, Biophysical Chemistry, **70**, 35-39 (1998).